Transforming inflammatory science and medicine

Clinical Trial Protocol

Study Title:	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of CTX-4430 Administered Orally Once-Daily for 48 Weeks in Adult Patients with Cystic Fibrosis
Study Number:	CTX-4430-CF-201
Study Phase:	2
Test Product:	CTX-4430
[redacted]	[redacted] [redacted] [redacted]
Indication:	Cystic Fibrosis
Sponsor:	Celtaxsys, Inc. 201 17th Street, Suite 530 Atlanta, GA 30363 United States
[redacted]	[redacted]

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SYNOPSIS

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Test Product: CTX-4430

Name of Active Ingredient: CTX-4430

Study Number: CTX-4430-CF-201	**Study Phase:** 2

Study Centers: up to 70 centers in the United States and Europe

Primary Objective:

- To evaluate the safety and tolerability of CTX-4430 administered orally once-daily to cystic fibrosis (CF) patients for 48 weeks
- To evaluate the efficacy of CTX-4430 administered orally once-daily to CF patients for 48 weeks as determined by the absolute change from Baseline in FEV_1 (forced expiratory volume in 1 second) percent predicted

Secondary Objectives:

- To evaluate the efficacy of CTX-4430 administered orally once-daily to CF patients for 48 weeks as determined by the relative change from Baseline in FEV_1 percent predicted
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on FVC (forced vital capacity) percent predicted and $FEF_{25-75\%}$ (forced expiratory flow during the middle half of the forced vital capacity) percent predicted
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on time to first pulmonary exacerbation while in the study
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on the number of pulmonary exacerbations
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on specified biomarkers (sputum DNA and elastase and serum high-sensitivity C-reactive protein [hs-CRP])

Exploratory Objectives:

- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on sputum bacterial density
- [redacted]
- To evaluate the change from Baseline in subject's health-related quality of life (HRQOL) while on CTX-4430 administered orally once daily for 48 weeks as measured by the Cystic Fibrosis Questionnaire - Revised (CFQ-R)

Study Design:

This study is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of CTX-4430 administered once-daily for 48 weeks for treatment of CF. A total of 195 pulmonary CF patients that meet all the inclusion and no exclusion criteria and provide written informed consent will be randomized to receive 50 mg CTX-4430, 100 mg CTX-4430, or placebo in a 1:1:1 ratio. Follow-up visits will be conducted approximately every 4 weeks from Week 4 to Week 52 (4 weeks after completion of treatment).

Spirometry will be performed at Screening, before the first dose and at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 52. Sputum will be induced and a sample collected before the first dose and at Weeks 8, 24, and 48 for measurement of DNA concentration, elastase concentration, and bacterial density (as measured by colony-forming units [CFUs]). A blood sample will be collected before the first dose and at Weeks 4, 8, 12, 24, 32, 40, 48, and 52 for measurement of hs-CRP. A pulmonary exacerbation criteria checklist will be completed before the first dose and at all subsequent study visits to the clinic or on the phone. [redacted] The CFQ-R will be administered before the first dose and at Weeks 12, 24, and 48.

[redacted]

Adverse events (AEs) and concomitant medications will be recorded from Screening to Week 52. Hematology, and urinalysis will be evaluated at Screening, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, 48, and 52. Serum chemistry will be evaluated at Screening, before the first dose and at Weeks 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, and 52. Weight and vital signs will be measured and pulse oximetry performed at all clinic visits. A complete physical exam will be performed at Screening and at Week 48. A physical exam focused on any medical complaints will be performed as required at all other visits. A 12-lead electrocardiogram (ECG) will be performed at Screening, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, and 48.

An Independent Data Monitoring Committee (IDMC) will periodically (approximately every 8 weeks) review the accumulating study data. The primary responsibility of the IDMC will be to monitor subject safety (including pulmonary exacerbations) and study conduct.

Number of Subjects Planned: 195 subjects

Diagnosis and Main Eligibility Criteria: patients aged 18 to 30 years (inclusive) with confirmed diagnosis of pulmonary CF and on a stable regimen of CF treatment with $FEV_1 \geq 50$ percent predicted and at least 1 acute pulmonary exacerbation in the 12 months prior to Screening

Duration of Treatment: 48 weeks

Test Product; Dose; and Mode of Administration: CTX-4430; 50 or 100 mg/day; oral capsule

Reference Therapy; Dose; and Mode of Administration: Placebo; oral capsule

Criteria for Evaluation:

Safety and Tolerability: AEs, concomitant medications, clinical laboratory evaluations (hematology, serum, chemistry, urinalysis), vital signs, weight, pulse oximetry, ECG parameters

Spirometry: FEV_1 (absolute value and percent predicted), FVC (percent predicted), $FEF_{25-75\%}$ (percent predicted)

Pulmonary Exacerbations: number of pulmonary exacerbations and time to pulmonary exacerbations, as defined by Fuchs criteria

Biomarkers: sputum DNA concentration, sputum elastase concentration, and serum hs-CRP concentration

Bacterial Density: presence/absence and quantitative counts (CFUs) of bacteria in sputum: *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex*, Achromobacter xylosoxidans, Stenotrophomonas maltophilia, and Staphylococcus aureus* (including methicillin–resistant *S aureus* and small colony variants of *S aureus*)

[redacted]

HRQOL: scores for respiratory and other domains of the CFQ-R

Statistical Methods:

Sample Size: A total of 195 subjects will be enrolled in trial to provide 52 evaluable subjects per treatment group in the Per-protocol Population (PP), assuming a drop-out rate of 20% in 48 weeks.

Primary Efficacy Analysis: The primary efficacy analysis of change from Baseline to Week 48 in FEV_1 percent predicted will be performed on the Full Analysis Population (defined as all randomized subjects receiving at least 1 dose of assigned treatment). The primary efficacy evaluation will compare the combined, average absolute change from Baseline in FEV_1 percent predicted of the 50 mg and 100 mg CTX-4430 treatment groups versus the placebo group.

The primary analysis will be based upon an analysis of variance (ANOVA) in which the average of the Week 48 change from Baseline in FEV_1 for the 2 CTX-4430 doses is compared to that in the placebo group. The ANOVA model will contain a separate term for each dose group with the average over the 2 CTX-4430 doses created by averaging the parameters estimates from the ANOVA model. In addition to terms for treatment group, the ANOVA will include stratification for the factors used for randomization. For subjects missing their Week 48 assessment, the average placebo change from Baseline to Week 48 will be imputed. Descriptive statistics will be presented by treatment group and averaged CTX-4430 dose.

If the primary analysis (aggregate CTX-4430 effect) reaches the 0.05 level of significance (1-sided), the individual CTX-4430 doses will be compared to the placebo arm using Dunnett's procedure at the 0.05 (2-sided) alpha level. This procedure maintains the type I error at the usual 0.05 (2-sided) level for the individual dose comparisons with placebo while allowing a proof of concept test for the pooled comparison at the 0.05 (1-sided). This approach is consistent with the Fleming and Richardson approach to Phase 2 screening trials in which a screening trial, if positive at the more stringent 0.05 2-sided level after preliminary testing, can

be treated as providing a more definitive statistical test and may reduce the amount of additional confirmatory trial data that is needed. No other adjustments for multiplicity will be used and other statistical analyses will be viewed as supportive.

Sensitivity analyses for the primary analysis will be conducted in which 1) the last available data is used (last observation carried forward), 2) the primary analysis is repeated using observed data only, and 3) using a rank based analysis where missing data are assigned the worst rank.

In addition to the univariate ANOVA, a mixed model repeated measures analysis of change from Baseline in FEV_1 percent predicted at each post-Baseline visit using all available data will be used to explore the consistency of the treatment effect over time. The model will include treatment (all 3 doses), visit, and treatment-by-visit interaction with additional factors for the randomization strata.

The primary analysis will be repeated on the PP as a supportive analysis.

Safety and Tolerability Analyses: The Investigator's verbatim term for each AE will be mapped to system organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment.

Concomitant medications will be coded using the most current WHO Drug Dictionary and summarized by drug class and medication term with results presented by treatment group.

Clinical laboratory results at each time point and change from Baseline will be displayed using summary statistics (n, mean, standard deviation [SD], median, minimum and maximum values) by treatment group. Listings of laboratory data will also be presented. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low. In addition, shift tables will be presented to display the shift in the normal range categories (low, normal, high) from Baseline to each specified time point. Baseline is defined as the latest result obtained prior to first investigational product (IP) administration.

Values at each time point and change from Baseline for weight, pulse oximetry, vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, and temperature), and ECG parameters will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each time point by treatment group. Baseline is defined as the latest result obtained prior to first IP administration. In addition, shift tables will be presented to display the shift in the normal range categories (abnormal/normal) from Baseline to each specified time point. Listings of these data will also be presented.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the time-concentration curve
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire - Revised
CFTR	cystic fibrosis transmembrane regulator
CFU	colony forming unit
C_{max}	maximum observed plasma concentration
CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ERS	European Respiratory Society
FAP	Full Analysis Population
$FEF_{25-75\%}$	forced expiratory flow during the middle portion of the forced vital capacity
FEV_1	forced expiratory volume in 1 second
5-LO	5-lipoxygenase
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
Hr	human recombinant
HRQOL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
IC_{50}	50% inhibition concentration

Abbreviation	Definition
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive Web randomization system
LTA4H	leukotriene A4 hydrolase
LTB4	leukotriene B4
NSAID	nonsteroidal anti-inflammatory drug
PK	pharmacokinetic
PP	Per-protocol Population
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
T_{max}	time at which maximum plasma concentration was observed
UGT	uridine glucuronosyltransferase triphosphate
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cell

1 INTRODUCTION

1.1 Cystic Fibrosis

Cystic fibrosis (CF) is one of the most important causes of chronic pulmonary disease. About 70,000 individuals are affected by CF worldwide.[1] The disease occurs in equal proportions in males and females.[2] CF is caused by mutation of the CF transmembrane regulator (CFTR) gene; the most common CFTR mutations are ΔF508, G542X, and G551D.[3] One in 29 Caucasian Americans and 1 in 25 people in the United Kingdom (UK) are carriers of a CFTR mutation.[1,4] Although mostly found in those of Caucasian descent, CFTR mutations do occur in other races but with lower frequency.[1] In the United States (US), 1 in 3400 children is born with CF,[1] and an estimated 30,000 individuals have CF (75% diagnosed by the age of 2 years).[1] In Europe, 1 in 2000 to 3000 children is born with CF,[5] and about 30,000 individuals have CF.[6] The median survival of someone with CF in the US is 37.4 years and in the UK 41 years.[1,2]

CF pathology is characterized by a cycle of infection, inflammation, and airway obstruction. Despite intensive treatment efforts to combat airway obstruction and infection, airway disease is the major cause of hospitalizations and death in the adult CF population. It is estimated that deaths from pulmonary complications of CF occur in over 80% of CF patients.[7] A study in France reported that the 1-year mortality rate for patients admitted to hospital for severe pulmonary exacerbations was 22%, and, for those admitted to the intensive care unit, the 1-year mortality rate was 48%.[7] Another recent study reported that 48% of CF patients were hospitalized for pulmonary exacerbations over a 26-month period.[8]

Leukotriene A4 hydrolase (LTA4H) is strongly implicated in the etiology of airway diseases, including CF [9,10]. LTA4H is a bifunctional enzyme with both epoxide hydrolase and aminopeptidase activities, catalyzing the formation of the ultimate pro-inflammatory mediator leukotriene B4 (LTB4) from LTA4. LTB4 is a powerful attractant and activator of inflammatory immune cells, particularly neutrophils. CF lung disease is characterized by significant neutrophilic infiltrates in the small airways and elevation of LTB4 in the airways.[11,12] In destructive pulmonary diseases such as CF, inhibition of LTB4 production has the potential to reduce both neutrophil influx and release of damaging neutrophil-derived enzymes such as elastase.[13,14]

Therapies aimed at decreasing the inflammatory response represent a relatively new strategy in the treatment of CF lung disease. Attention has focused primarily upon the therapeutic potential of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). Although often beneficial, the use of systemic corticosteroids is limited by their unacceptable adverse effects. Although inhaled corticosteroids are used in CF, it is unclear if they are effective. High-dose ibuprofen has been shown to target CF lung inflammation, resulting in increased forced expiratory volume in 1 second (FEV_1) and decreased neutrophilic lung infiltrates in adults and a slower rate of FEV_1 decline in children.[15,16] However, because of gastrointestinal effects including bleeding, its use has not been widely adopted.

The most recent advance in the treatment of CF is modulation of the abnormal CFTR protein. Currently, ivacaftor is the only CFTR therapy approved for the treatment of CF.[17] It is indicated only for the small percentage of CF patients (approximately 6%) who have the G551D and

functionally similar gating mutations. Trials with correctors and potentiators for other classes of CFTR genetic mutations (such as ataluren) and with combinations of correctors and potentiators (such as the ivacaftor/lumacaftor combination [18]) are ongoing. However, even these targeted therapies may not address the dysregulated inflammatory response, as exemplified by the GOAL study.[19]

Thus, there is a clear unmet need for additional treatment options for CF lung disease, particularly those that address the underlying inflammation in a safe and effective manner, and can be used concomitantly with other medications for CF. The involvement of neutrophils and critical role of LTB4 suggests that inhibition of LTA4H is a reasonable potential target for further clinical evaluation.

1.2 CTX-4430

CTX-4430 is a novel synthetic, small-molecule, LTA4H inhibitor being developed to address the underlying pulmonary inflammation in CF. CTX-4430 inhibits both the epoxide hydrolase and the aminopeptidase activities of LTA4H in vitro. CTX-4430 has also shown inhibition of LTB4 production after oral administration in both animal and human studies.

1.2.1 Nonclinical Studies of CTX-4430

A full battery of pharmacology, pharmacokinetic (PK), and toxicology studies has been conducted, including studies of genetic, juvenile, and reproductive toxicology. Key findings are summarized below. Additional details of the nonclinical studies can be found in the current Investigator Brochure (IB).

The pharmacologic effect of CTX-4430 correlates directly with plasma drug levels, suggesting no significant lag or persistence of effect. Trough plasma levels sufficient to achieve 50% or greater inhibition of LTB4 production have been associated with therapeutic effects in a number of inflammatory disease models. Nonclinical pharmacokinetic and metabolism studies indicated that CTX-4430 is rapidly absorbed in the upper intestine by passive transit across the gut tissue and then distributed throughout the water compartment of the body. CTX-4430 is eliminated predominantly intact as parent drug (>90%) via the liver to bile to feces route with only a small amount of parent drug (<3%) and metabolites appearing in urine. CTX-4430 was also evaluated for inhibition of human recombinant (hr) uridine glucuronosyltransferase triphosphate (UGT) enzymes UGT1A1 and UGT2B7. The values for the 50% inhibition concentration (IC_{50}) for hrUGT2B7 and hrUGT1A1 were >125 μM, suggesting that at these concentrations the risk of inhibition by CTX-4430 is low. CTX-4430 is not a significant substrate or inhibitor of cytochrome P450 (CYP) enzymes or other transporters. In vitro studies suggest CTX-4430 may be a weak substrate of P-glycoprotein, a weak inhibitor of transporters OAT3, OCT2, and OATP1B1, or a weak inducer of CYP2B6.

Pharmacological safety studies showed a low potential for acute adverse effects of CTX-4430 at human-equivalent oral doses below 649 mg/day. Signs of acute overdose may include non-life-threatening, self-resolving changes in heart rate and blood pressure with concomitant electrocardiogram (ECG) changes that may be associated with nonlethal, self-resolving convulsion. Long-term toxicity studies in animals suggested safe chronic administration of oral

doses up to 200 mg/day in adult humans. On the basis of the nonclinical toxicity studies, signs of chronic toxicity in humans may include reduced food consumption, lack of body weight gain, or body weight loss. The toxicity of CTX-4430 in juvenile animals was similar to that observed in adult animals.

No evidence of mutagenicity or clastogenicity was observed in genotoxicity assays, suggesting that CTX-4430 has low potential for these effects in humans. In nonclinical reproductive toxicity studies, CTX-4430 did not exhibit adverse effects on fertility, implantation, or embryofetal development at any dose level tested. Therefore, on the basis of the nonclinical studies conducted to date, chronic doses up to 200 mg/day are reasonably expected to be safe in humans aged 2 years and older.

1.2.2 Clinical Trials of CTX-4430

Three studies have been conducted in humans:

- CTX-4430-HV-001: A Phase I, Randomised, Double-Blind, Placebo-Controlled, Ascending Single- and Repeat-Dose Study of the Safety, Tolerability and Pharmacokinetics of CTX-4430 when Administered Orally to Healthy Adult Subjects with Two Single-Dose Groups Crossing over to Assess Food Effect
- CTX-4430-CF-001: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Ascending Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CTX 4430 when Administered Orally to Cystic Fibrosis Patients for Fifteen Days
- CTX-4430-DI-001: A Phase 1, Open-Label, Two-Period, Fixed-Sequence, Drug-Drug Interaction Study to Evaluate the Pharmacokinetics and Safety of CTX-4430 and Midazolam in Healthy Adult Subjects

The results of these clinical trials are summarized below, and additional details can be found in the current IB.

In the clinical development program to date, 68 subjects (including 12 CF patients) have received multiple doses of CTX-4430 for 14 or 15 days. PK results from these multiple-dose studies in healthy volunteers and in CF patients showed that the PK parameters were largely similar between these 2 populations. CTX-4430 is relatively rapidly absorbed, achieving maximum observed plasma concentration (C_{max}) within 1 to 2 hours after oral dosing in the fasted state. The estimated elimination half-life ranged from approximately 9 hours in CF patients to approximately 16 hours in healthy volunteers. The reason for this difference is not known; however, it had no effect on C_{max} and only a small effect (20% difference) on the area under the time-concentration curve (AUC).

Food delayed the median time at which maximum plasma concentration was observed (T_{max}) but had only a slight effect on C_{max} or AUC. After single 50 or 100 mg doses, mean T_{max} increased approximately 3-fold (to 5.7 and 4.4 hours, respectively) while the mean C_{max} decreased by 22% for 50 mg and by 36% for 100 mg. The mean AUC increased by 28% after the 50 mg dose and decreased by 21% following the 100 mg dose. These results suggest that food affects the rate but not the extent of absorption.

Steady state was reached by Day 7 in all 3 Phase 1 studies conducted to date. At steady state, mean AUC, C_{max}, and C_{min} (minimum observed plasma concentration) increased approximately 1.5- to 2-fold over the values observed after the first 100 mg dose in both healthy volunteers and CF patients.

The increase in systemic exposure (C_{max}, concentration at steady state, and AUC) with dosage was nonlinear in the healthy volunteers, increasing in a slightly greater than proportional manner. In contrast, exposures after doses of 50 and 100 mg/day in CF patients were largely dose-proportional.

A drug-drug interaction study to assess the potential for CTX-4430 to induce CYP3A4/5 showed that CTX-4430 does not induce CYP3A4/5 activity in vivo and can thus be administered before CYP3A4- and CYP3A5-metabolized drugs (such as midazolam) without perpetrating a significant drug-drug interaction.

Blood pharmacodynamics were studied in both healthy volunteers and CF patients. Plasma levels of CTX-4430 at peak and trough showed large multiples over the whole-blood IC_{50} for LTB4 inhibition and concomitantly suppressed LTB4 production to a significant degree at doses of 50 mg/day and higher. In healthy volunteers, the 100 mg dose yielded near maximal suppression of LTB4 production in blood. For reasons that are not yet known, similar plasma levels of CTX-4430 at the 100 mg dose level in CF patients yielded suppression of LTB4 production in blood (approximately 70% maximum inhibition) that was lower than that observed for healthy volunteers (greater than 80 maximum inhibition).

Encouraging trends in blood and sputum biomarkers of inflammation were observed in CF patients in the Phase 1 study. Correlated reductions in sputum LTB4 (a marker for the CTX-4430 mechanism), sputum DNA (a marker for neutrophil infiltration in CF lung), sputum elastase (a marker for neutrophil activity and tissue degradation in CF lung), and serum C-reactive protein (a marker for systemic inflammation) were observed in the subjects who received active CTX-4430 as compared both to values in subjects in the placebo group and to their own Baseline values. Most notable among these effects were reductions in sputum white blood cells (WBCs) and neutrophils for the entire CTX-4430 treated group. For sputum WBC, there was a 31% reduction from Baseline in the treated group as a whole and a 60% reduction from Baseline in the 100 mg CTX-4430 group. For sputum neutrophils, there was a 34% reduction from Baseline in the treated group and a 65% reduction from Baseline in the 100 mg CTX-4430 group.

To date, CTX-4430 has been well tolerated by healthy volunteers at doses up to 200 mg once-daily for 14 days. It has also been well tolerated at doses of 50 and 100 mg for 15 days in CF patients. There were no clinically relevant trends in vital signs, clinical laboratory values (including hematology and clinical chemistry), and the ECG results. The most common treatment-emergent adverse events (TEAEs) on multiple dosing with 50 mg or 100 mg of CTX-4430 were headache, abdominal pain or discomfort, oropharyngeal pain, cough, increased sputum, and hemoptysis. None of the TEAEs in these multiple-dose studies were considered definitely related to CTX-4430 by the Investigators. The highest degree of relatedness to CTX-4430 assessed for TEAEs in these studies was an assessment of probably related for a headache in a subject taking 50 mg CTX-4430. Headache was the most common adverse event considered by the investigators to be related to the use of CTX-4430 (13%). There was no dose

relationship in incidence or severity of TEAEs, and most of the events were mild or moderate in severity. There were no deaths in the Phase 1 studies. One subject with CF who received CTX-4430 experienced a serious adverse event (SAE) of pulmonary exacerbation requiring hospitalization that was unlikely related to CTX-4430 and occurred 35 days after the last dose. No subjects who received CTX-4430 withdrew from the study because of a TEAE.

[redacted] Based on the clinical data in healthy volunteers and CF patients, once-daily oral doses of 50 and 100 mg are suitable for study in subsequent clinical trials of CF. These doses exhibit good safety and tolerability as well as a range of pharmacologic effects in humans relevant to patients with CF and thus provide a basis for the initial assessment of longer-term safety and potential efficacy of CTX-4430 for treatment of CF.

2 OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and tolerability of CTX-4430 administered orally once-daily to CF patients for 48 weeks
- To evaluate the efficacy of CTX-4430 administered orally once-daily to CF patients for 48 weeks as determined by the absolute change from Baseline in FEV_1 (forced expiratory volume in 1 second) percent predicted

2.2 Secondary Objectives

- To evaluate the efficacy of CTX-4430 administered orally once-daily to CF patients for 48 weeks as determined by the relative change from Baseline in FEV_1 percent predicted
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on FVC (forced vital capacity) percent predicted and $FEF_{25-75\%}$ (forced expiratory flow during the middle portion of the forced vital capacity) percent predicted
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on time to first pulmonary exacerbation while in the study
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on the number of pulmonary exacerbations
- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on specified biomarkers (sputum DNA and elastase and serum high-sensitivity C-reactive protein [hs-CRP])

2.3 Exploratory Objectives

- To evaluate the effect of CTX-4430 administered orally once-daily to CF patients for 48 weeks on sputum bacterial density
- [redacted]
- To evaluate the change from Baseline in subject's health-related quality of life (HRQOL) while on CTX-4430 administered orally once daily for 48 weeks as measured by the Cystic Fibrosis Questionnaire - Revised (CFQ-R)

3 STUDY DESIGN

3.1 Overall Study Design

This study is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of CTX-4430 administered once-daily for 48 weeks for treatment of CF. A total of 195 pulmonary CF patients that meet all the inclusion and no exclusion criteria and provide written informed consent will be randomized to receive 50 mg CTX-4430, 100 mg CTX-4430, or placebo in a 1:1:1 ratio. Follow-up visits will be conducted approximately every 4 weeks from Week 4 to Week 52 (4 weeks after completion of treatment).

Spirometry will be performed at Screening, before the first dose and at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 52. Sputum will be induced and a sample collected before the first dose and at Weeks 8, 24, and 48 for measurement of DNA concentration, elastase concentration, and bacterial density (as measured by colony-forming units [CFUs]). A blood sample will be collected, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, 48, and 52 for measurement of hs-CRP. A pulmonary exacerbation criteria checklist will be completed before the first dose and at all subsequent study visits to the clinic or on the phone. [redacted] The CFQ-R will be administered before the first dose and at Weeks 12, 24, and 48.

[redacted] There will be no genetic tests done on any samples taken in this study.

Adverse events (AEs) and concomitant medications will be recorded from Screening to Week 52. Hematology, and urinalysis will be evaluated at Screening, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, 48, and 52. Serum chemistry will be evaluated at Screening, before the first dose and at Weeks 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, and 52. Weight and vital signs will be measured and pulse oximetry performed at all clinic visits. A complete physical exam will be performed at Screening and at Week 48. A physical exam focused on any medical complaints will be performed as required at all other visits. A 12-lead ECG will be performed at Screening, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, and 48.

An Independent Data Monitoring Committee (IDMC) will periodically (approximately every 8 weeks) review the accumulating study data. The primary responsibility of the IDMC will be to monitor subject safety (including pulmonary exacerbations) and study conduct.

3.2 Rationale for Study Design

3.2.1 Study Population

The study population consists of patients with documented pulmonary CF, a planned target population for CTX-4430. The population included in this study (CF patients with ≥50% FEV_1 at Baseline and at least 1 pulmonary exacerbation in the prior year) was chosen for its high rate of

annual decline in FEV_1, with an expected mean annual decline in FEV_1 percent predicted of 3.3% to 5.1% as shown in Table 1.

Table 1 Annual Change in FEV_1 in CF Patients Aged 18 to 30 Years

Baseline FEV_1 Range (Percent Predicted)	N	Mean	25% Percentile	50% Percentile	75% Percentile
50 to 59	531	-3.3	-6.8	-3.0	0.7
60 to 79	965	-3.3	-7.5	-2.9	1.2
80 to 99	598	-3.8	-7.0	-3.2	0.5
≥100	94	-5.1	-8.0	-3.0	0.1

Source: Cystic Fibrosis Foundation registry data.

According to Konstan et al, high-dose ibuprofen significantly stems the annual rate of decline of FEV_1, showing approximately 1.5% improvement in annual decline of FEV_1 percent predicted vs placebo ($P = 0.02$). [20] While seemingly small in magnitude, this improvement represents a 40% reduction in rate of decline or effectively sparing of nearly 5 months of lung function year over year. The effect of high-dose ibuprofen on rate of FEV_1 decline was attributed to its anti-inflammatory activity via the inhibitory effect on neutrophil activation and migration via the LTB4 pathway. [15,21] Inhibition of LTA4H by CTX-4430 can have a similar effect on neutrophils and over the course of 48 weeks could have a positive effect on decline in FEV_1 percent predicted as compared to placebo.

3.2.2 Study Treatments

The 50 mg and 100 mg doses of CTX-4430 were selected for this study because these doses showed consistent reduction of LTB4 levels in CF patients in study CTX-4430-CF-001. Repeated dosing of 50 mg and 100 mg for 14 days in healthy volunteers and in CF patients for 15 days produced an acceptable safety profile and was well tolerated. CTX-4430 has been administered to rats in doses up to 100 mg/kg/day for 6 months and to dogs in doses up to 6 mg/kg/day for 9 months. The no-observed-adverse-effect level in the most sensitive species (dog) was 6 mg/kg day, corresponding to a human equivalent dose of 195 mg/day. CTX-4430 exposure at this dose in the dog study was greater than or equivalent to the exposure at 200 mg in the healthy volunteer human study CTX-4430-HV-001. Thus, the 50 and 100 mg once-daily oral doses chosen for this study are well-supported by the chronic nonclinical toxicology studies, exhibit adequate safety and tolerability in human studies conducted to date, and demonstrate pharmacological effects in humans relevant to CF disease.

Matching placebo was selected as the control for optimal assessment of the safety and efficacy of CTX-4430.

A trial of 48 weeks is warranted for study of anti-inflammatory treatments in CF, even at the Phase 2 stage, since the expected major impact of this class of treatment will be to reduce the rate decline in FEV_1. Current Cystic Fibrosis Foundation registry data (Table 1) indicate that the expected rate of FEV_1 decline is in the range of 3.3 to 5.1 % per year. Variability (as coefficient of variation, CV) of FEV_1 percent predicted in CF trials typically ranges from 7 to 10%, meaning that CV will be on the order of twice the size of the anticipated FEV_1 change over the course of a year. Thus, 48 weeks is the optimum duration for discerning an effect on rate of FEV_1 decline

that enables projection of anticipated effect size and powering for Phase 3 studies while minimizing total patient enrollment in Phase 2. This duration is consistent with precedent for CF treatments considered to be anti-inflammatory, as described in Table 2.

Table 2 Anti-inflammatory Treatments for CF

Drug	Mechanism	N	Duration (Weeks)	Outcomes		
				Biomarker	FEV_1	Acute Pulmonary Exacerbations
AZD9668	Elastase inhibition	56	4	No reduction in sputum elastase or PMNs but reduction in IL-6 and RANTES	No effect	Not reported
SB-656933	IL-8 antagonism	146	4	Trend to reduction of sputum elastase, DNA, PMNs	No effect	Not reported
Azithromycin [a]	Unknown	260	24	Not reported	73% reduction in rate of decline (-0.5% vs -1.9%)	50% reduction
NAC	Glutathione enhancement	70	24	No reduction in sputum elastase	6% increase mostly driven by reduction in decline compared to placebo (+1.1% vs -5.6%)	Not reported
High-dose ibuprofen	LTB4 inhibition	85	192	Not reported	40% reduction in rate of decline (-2.17% vs -3.6%); 58% reduction in rate in compliant subjects (-1.48% vs -3.57%)	No change in number of hospitalizations

DNA = deoxyribonucleic acid; IL-6 = interleukin 6; IL-8 = interleukin 8; LTB4 = leukotriene B4; NAC = N-acetylcysteine; PMN = polymorphonuclear leukocytes; RANTES = regulated upon activation, normal T-cell expressed and secreted.

[a] No subjects with *Pseudomonas aeruginosa*

Sources: References 20,22,23,24,25.

Short (4 weeks) studies have been attempted for evaluation of anti-inflammatory treatments in CF but have resulted in an inability to observe changes in FEV_1 sufficient to guide Phase 3 design. Longer (≥24 weeks) studies have been more informative but have either been excessively long (as with high-dose ibuprofen) or reliant on an unusually high rate of decline (as with N-acetylcysteine). The most relevant example is that of azithromycin tested in patients not infected with *Pseudomonas aeruginosa*, which showed a rate of FEV_1 decline in the placebo group (1.94% in 6 months) consistent with current annual rates of decline. In this case, azithromycin reduced FEV_1 decline compared to placebo by 1.4% in 24 weeks. This decline projects to a 73% reduction in rate of decline compared to placebo and a 2.8% improvement in annual rate of FEV_1 decline, which would be clearly significant outcomes for CF patients. However, because of the small effect size (1.4%) even with a large patient sample (125 per cohort), the change in FEV_1 did not approach statistical significance sufficiently ($P = 0.34$) to be deemed a meaningful outcome for progression to Phase 3. Thus, a trial of 48 weeks is required

for observation of sufficient change in FEV_1 to assess the therapeutic effect of drugs with anti-inflammatory effect in CF.

3.2.3 Study Endpoints

The primary, secondary, and exploratory efficacy endpoints in this study are aligned with academic and regulatory endpoints for the clinical development of a treatment for CF.[26]

Pulmonary exacerbations are defined as treatment with oral, inhaled, or intravenous (IV) antibiotic(s) for ≥4 of symptoms/signs per the criteria of Fuchs et al,[27] (modified Fuchs criteria) the standard definition used in clinical trials of CF.[28]

The exploratory endpoint of HRQOL will be evaluated using the CFQ-R, a validated disease-specific HRQOL measure for children, adolescents, and adults with CF.[29,30,31] It is a profile measure of HRQOL with several different domains, including physical functioning, vitality, health perceptions, respiratory symptoms, treatment burden, role functioning, emotional functioning, and social functioning.

3.3 Independent Data Monitoring Committee

An IDMC will be formed to periodically (approximately every 8 weeks) review the accumulating study data. The primary responsibility of the IDMC will be to monitor subject safety (including pulmonary exacerbations) and study conduct. The IDMC will have access to both safety and efficacy data. The IDMC will be requested to avoid formal evaluations of efficacy for the purpose of discontinuing the trial early for benefit. As such, no adjustment for multiple testing will be required. The IDMC will review the study data in accordance with a written charter.

3.4 Study Duration

The duration of enrollment is estimated to be 13 months; the actual duration of enrollment may be longer. Each subject will be followed for approximately 52 weeks after enrollment, so the duration of the study is estimated to be about 25 months.

4 SUBJECT POPULATION

4.1 Inclusion Criteria

Patients are eligible to participate in the study if they meet all of the following inclusion criteria:

1. 18 to 30 years of age inclusive at the time of Screening
2. Documented, confirmed diagnosis of pulmonary CF (defined as follows):
   - CF signs and symptoms AND
   - Either 2 CFTR mutations on genetic testing OR sweat chloride ≥60 mEq/L
3. Medically stable, in the Investigator's opinion
4. At least 1 pulmonary exacerbation, based on the Investigator's judgment, in the 12 months before Screening
5. Resolution of any pulmonary exacerbation of CF at least 14 days before Screening, in the Investigator's opinion
6. On a stable regimen of CF treatments with no change for at least 14 days before Screening and between Screening and Baseline
7. If on ivacaftor or ivacaftor-lumacaftor combination, on a stable regimen for at least 8 weeks before Baseline
8. No clinical or radiological evidence, per the Investigator's site procedures, of clinically significant lung abnormalities (e.g., major atelectasis, pneumothorax)
9. FEV_1 ≥50 percent predicted at Screening
10. Resting oxygen saturation >92% on room air
11. Body mass index (BMI) ≥17.0 kg/m^2
12. No smoking (including electronic cigarettes) for at least 6 months before Screening and agreement not to use such products for the duration of the study
13. Females of childbearing potential must have a negative pregnancy test at Screening (unless surgically sterile) and must agree to use an effective contraception method from screening throughout the duration of the study (refer to Section 5.10.2 for definition of acceptable effective methods).
14. Able to perform spirometry according to European Respiratory Society/American Thoracic Society guidance [32]
15. Able to swallow investigational product (IP) whole
16. Able to comply with the study procedures, in the opinion of the Investigator
17. Has provided informed consent to participate in the study

4.2 Exclusion Criteria

Patients are eligible to participate in this study if they meet none of the following exclusion criteria:

1. In the opinion of the Investigator, any significant clinical/laboratory/radiological/spirometric sign of unstable or unexpectedly deteriorating respiratory disease within 14 days before Screening or between Screening and Baseline (These clinical/laboratory/radiological/ spirometric signs include, but are not limited to, features suggestive of a pulmonary exacerbation as suggested by the modified Fuchs' criteria.)
2. A medical condition that is unstable, could be adversely impacted by participation in the study, or could impact assessment of the study results, in the opinion of the Investigator
3. History of organ transplantation
4. History of either alcoholism or drug abuse in the opinion of the investigator
5. Clinically significant hemoptysis (e.g., > approximately 30 cc per episode, or clinically significant in the Investigator's opinion) within 180 days before Screening
6. Colonization with organisms associated with a more rapid decline in respiratory function in CF patients (e.g. all *Burkholderia* species, *Mycobacterium abscessus)*. Subjects with a history of a positive culture could be considered free of colonization if she/he has had 6 subsequent respiratory tract cultures negative for these bacteria within the past 24 months prior to Screening, with one of these cultures obtained within 6 months prior to Screening
7. Active allergic bronchopulmonary aspergillosis at Screening or at Baseline
8. Any clinically significant ECG abnormality, in the Investigator's opinion
9. Positive serology for HIV-1 or HIV-2 antibody, hepatitis C virus antibody, or hepatitis B surface antigen at Screening
10. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$2 × the upper limit of normal (ULN) at Screening
11. Bilirubin >1.25 × ULN at Screening. Subjects with known Gilbert's syndrome can be included with bilirubin >1.25 x ULN
12. Any subject with cirrhosis of the liver
13. Any subject with portal hypertension
14. Neutrophil count <1.5 × 10^9/L at Screening
15. Platelet count <150,000/µl at Screening
16. Clinically unstable pancreatic function, in the opinion of the Investigator. Evidence of unstable pancreatic function could include:
    - Clinically significant weight loss (≥5% after a previously stable period)
    - Evidence of uncontrolled hyperglycemia or recent hypoglycemia
    - Change in pancreatic enzyme requirements in the 60 days before Screening

17. Use of systemic corticosteroids, or systemic antimicrobial therapy (other than chronic antimicrobial use, e.g. azithromycin, flucloxacillin, itraconazole) within 14 days before Screening or between Screening and Baseline
18. Regular use (>3 times per week) of a high-dose NSAID (e.g., >1.6 g ibuprofen/day) within 60 days before Screening or between Screening and Baseline
19. Participation in a clinical trial for any medical/device product within 30 days before Screening (participation in a noninterventional or observational study is permitted)
20. Pregnant or nursing women

5 INVESTIGATIONAL PRODUCTS

5.1 CTX-4430

CTX-4430 (drug substance) is 4-[[(1S,4S)-5-[[4-[4-(2-oxazolyl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]-benzoic acid. It is a chiral molecule that is manufactured as a single isomer (S, S configuration) that does not racemize. In solution, CTX-4430 behaves as a zwitterion with a terminal carboxyl group and a tertiary amine group.

CTX-4430 is formulated as a powder blend in size 0 hard gelatin capsules of 50 mg or 100 mg dosage strength per capsule for oral administration. Excipients are mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, and silicon dioxide. Each bottle contains 36 capsules.

5.2 Placebo

Placebo capsules are identical to the CTX-4430 capsules except that they do not contain the drug substance.

5.3 Packaging and Labeling

CTX-4430 and placebo are packaged in 75 cc capacity round, white high-density polyethylene (HDPE) bottles fitted with a 38 mm white, screw-top HDPE closure. Each bottle contains 36 capsules and is labelled in accordance with national requirements for clinical trial supplies.

5.4 Storage

IP should be stored in the containers in which they are supplied at controlled room temperature (15°C to 25°C / 59°F to 77°F), and protected from ultraviolet light.

Each investigational site will keep a regular record of maximum and minimum temperature readings in the IP storage area throughout the conduct of the study.

5.5 Screening

The Screening Period will occur within 21 days before the first dose of study drug to confirm that subjects meet the selection criteria for the study. The assessments to be conducted are shown in 6.3.1. The investigator (or an appropriate authorized designee) will obtain informed consent from each subject.

Based on investigator's judgement, borderline abnormal laboratory tests which may exclude the subject, may be repeated once within 7 days of the screening visit without the subject being considered a screen fail. The medical monitor must be consulted for approval in such cases.

In addition, subjects who fail to meet the ATS/ERS criteria for quality (acceptability, reproducibility, and end of test criteria) at screening may be retested once without being considered a screen failure. This retest should occur at least one day after the initial screening

visit and should be completed within 7 days of the original screening visit date. Final decision on screen failure will be based upon FEV1 data after review with the medical monitor.

Rescreening:

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated. Subjects may only be rescreened once. If a subject is rescreened, the screening window begins at that time.

5.6 Randomization

Upon determination that a subject meets all eligibility criteria, the subject will be randomized to treatment assignment via an interactive Web randomization system (IWRS). Each subject will be assigned to CTX-4430 50 mg, CTX-4430 100 mg, or placebo in a blinded 1:1:1 fashion by means of a computer-generated randomization list stratified by Baseline FEV_1 percent predicted (50 to 75% and >75%), number of pulmonary exacerbations in the 12 months before Screening (1 or >1), and use of CFTR-modulating therapy such as ivacaftor or lumacaftor (yes/no).

5.7 Blinding and Unblinding

Investigators, subjects, and all study staff with direct subject contact will be blinded to treatment assignment. All Celtaxsys study team staff members and contract research organization study team members will remain blinded unless specifically designated as unblinded and independent from the study team. Such independent, unblinded study personnel may include drug distribution and IWRS vendor staff. Pharmacovigilance staff will be unblinded as necessary for reporting to regulatory authorities, with appropriate controls to assure that access to any unblinded information is restricted to the safety reporting staff. The sponsor will maintain a list of any designated individuals at the vendors or sponsor that are designated as unblinded.

The investigator will ensure that blinding is broken only in accordance with the protocol conditions for unblinding due to medical necessity or safety reasons.

In the case of a medical emergency, where the appropriate treatment of the subject requires knowledge of the IP, CTX-4430 or placebo, the investigator may break the randomization code at any time for an individual subject through the IWRS system. Detailed procedures to break the blind will be provided to the investigator. In such cases, the AE necessitating the emergency blind break will be clearly justified, explained in writing, captured on the SAE form (if due to a SAE) in accordance with the procedures indicated in section 8.6., and must be reported to the medical monitor immediately. The Sponsor medical team, for matters relating to safety concerns and associated regulatory reporting, may unblind individual subjects at any time.

5.8 Administration of Investigational Products

The first dose of IP will be taken at the investigational site during Visit 2 (Baseline). Thereafter, the subject will take a capsule each day with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

5.9 Concomitant Medications

Chronic use of systemic corticosteroids, and regular use (>3 times per week) of high-dose NSAIDs (e.g., >1.6 g ibuprofen/day) is prohibited during the study. If a need for any of these treatments arises during the study, the subject must be discontinued from the study.

All concomitant medications, including over-the-counter medicines, will be reported in the electronic case report form (eCRF).

5.10 Other Study Restrictions

5.10.1 Subject Activity Restrictions

Subjects must not smoke during the study.

5.10.2 Contraception

Women of childbearing potential must use an effective method of contraception until 28 days after taking the last dose of IP. Acceptable effective methods of contraception include the following methods:

1. Monogamous relationship with vasectomized partner,

2. Licensed hormonal methods associated with inhibition of ovulation (e.g., combination oral contraceptive pills, progestin-only hormonal contraception that inhibits ovulation)

    - For women who are receiving ivacaftor-lumacaftor combination therapy, hormonal contraception, including oral, injectable, transdermal and implantable, is considered to be unreliable and hence cannot be used as an effective method of contraception. In such patients who are on hormonal contraception, one of the following barrier methods of contraception should be added; male condom, diaphragm, cervical cap or female condom.

3. Intrauterine contraceptive devices (including intrauterine hormonal systems).

4. True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject, can be considered an effective method of contraception based on the judgement of the investigator. Periodic abstinence is not an acceptable method of contraception.

Based on the investigator's judgement, the following acceptable methods of contraception may also be used:

1. Double barrier methods of contraception, which is the use of a male condom plus either diaphragm or cervical cap, may be allowed. The male condom cannot be used with a female condom as a double barrier method of contraception due to risk of tearing.

2. Male or female condom plus a spermicide, or diaphragm plus a spermicide may be allowed (acceptable methods if spermicide is regionally available)

If local regulations require the use of additional contraceptive measures, these must be followed.

5.11 Compliance

An investigational site staff member will count the capsules returned by each subject at Visits 3, 5 to 9, 11, 13, and 15 and record the number of capsules returned. Subjects will be questioned in relation to any capsules which may have been lost or destroyed to gain a full understanding of the number of capsules taken during the treatment period.

6 STUDY PROCEDURES

Refer to Appendix 1 for the Schedule of Events.

6.1 Blood Sample Volume

Table 3 Total Blood Volume Collected from Subjects During the Study

Sample Type	Number of Sampling Time Points	Volume per Time Point	Total Volume
Screening laboratory tests: hematology, serum chemistry, serology, serum pregnancy (for women of childbearing potential only)	1	~ 15 mL	~ 15 mL
Hematology	9	~ 10 mL	~ 90 mL
Serum chemistry (may include hs-CRP)	12	~ 5 mL	~ 60mL
[redacted]	[redacted]	[redacted]	[redacted]
		Total blood volume	~ 215 mL

hs-CRP = high-sensitivity C-reactive protein, [redacted]

6.2 Guidelines for Study Procedures

6.2.1 Administration of CFQ-R

Administered before spirometry, and collection of sputum, blood, and urine samples. The CFQ-R will be administered by the site staff.

6.2.2 Adverse Events

See Section 8.

6.2.3 Body Mass Index

Calculated as follows: weight (kg)/height $(m)^2$.

6.2.4 Complete Physical Examination

Examination performed by a licensed health care provider of, at a minimum, the following systems: skin, head, ears, eyes, nose and throat, respiratory, cardiovascular, gastrointestinal, neurological, musculoskeletal, and lymphatic systems.

6.2.5 Focused Physical Examination

Examination performed by a licensed health care provider according to subject's medical history and complaints.

6.2.6 Hematology

Hematocrit, hemoglobin, platelets red blood cell count, WBC count with differential, and absolute neutrophil count.

[redacted]

6.2.8 Pulmonary Exacerbation Checklist

Pulmonary exacerbations are defined as treatment with oral, inhaled, or IV antibiotic(s) for ≥4 of symptoms/signs listed below per the modified Fuchs criteria [27]. The date of onset of the pulmonary exacerbation will be recorded, which will be defined as the date of initiation of antibiotics for the pulmonary exacerbation. The pulmonary exacerbation checklist will capture the signs/symptoms listed below as well as the treatment with oral, inhaled, or IV antibiotics:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature >38°C
- Anorexia or weight loss

- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- 10% or more absolute decrease in FEV_1 percent predicted from the previously recorded value
- Radiographic changes indicative of pulmonary infection

6.2.9 Serum chemistry

Albumin, alkaline phosphatase, ALT, AST, GGT, bicarbonate, bilirubin (total and direct), blood urea nitrogen, calcium, chloride, creatinine, glucose, phosphorus (phosphate), potassium, sodium, uric acid, total protein, and hs-CRP

6.2.10 Spirometry

Spirometry will be performed before the sputum induction procedures.

Subjects should take their concomitant medications as per their usual schedule. However, any short-acting bronchodilator (e.g. albuterol) should not be taken within 4 hours of scheduled time for spirometry, and any long-acting bronchodilator should not be taken within 12 hours (e.g. salmeterol) or 24 hours (e.g. tiotropium bromide) of scheduled time for spirometry. Every effort will be made to perform all tests for a given subject at the same time of day ±1 hour from the time of the Baseline measurement with the supplied study specific spirometry equipment. If possible, the same respiratory technician should conduct all tests for a subject. Efforts should be made to ensure a consistent approach to subject coaching to minimize variation during spirometry. It is essential to have reproducible "research grade" spirometry throughout the duration of the study. Operators will coach subjects to ensure optimal effort is achieved. If optimal results are not obtained after 4 attempts the subject should rest for 10 minutes before an additional maximum of 4 efforts are conducted. Further detail and instruction will be provided in the Pulmonary Function/Spirometry manual.

Subjects who fail to meet the ATS/ERS criteria for quality (acceptability, reproducibility, and end of test criteria) at screening may be retested once without being considered a screen failure. This retest should occur at least one day after the initial screening visit and should be completed within 7 days of the original screening visit date. For other visits, if a subject fails to adhere to protocol requirements, (e.g. bronchodilator use) or fails to meet ATS/ERS criteria for quality, then at the discretion of the investigator, the spirometry may be repeated once. The retest should occur at least one day after the initial visit but as soon as possible up to a maximum of 7 days.

6.2.11 Sputum Induction and Sample Collection

The sputum induction and collection process will follow the Therapeutic Development Network Standard Operating Procedure (SOP) in the US and the Clinical Trials Network SOP in Europe. Any deviation from these SOPs will require prior approval from the Sponsor and will need to be documented.

The subject will be given 2 sterile jars of adequate volume to collect the sputum.

6.2.12 Urinalysis

Macroscopic evaluation of bilirubin, blood, glucose, ketones, leukocyte esterase, nitrites, pH, protein, and specific gravity

6.2.13 Urine Alcohol and Drug Screen

Alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates

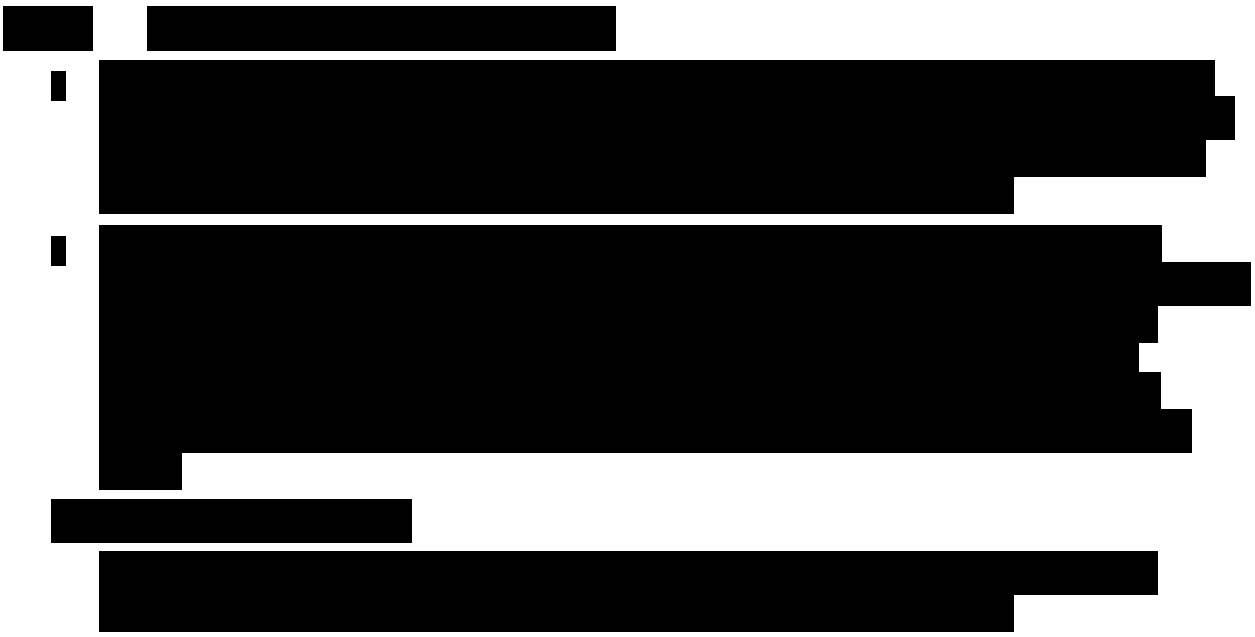
6.2.14 Vital Signs

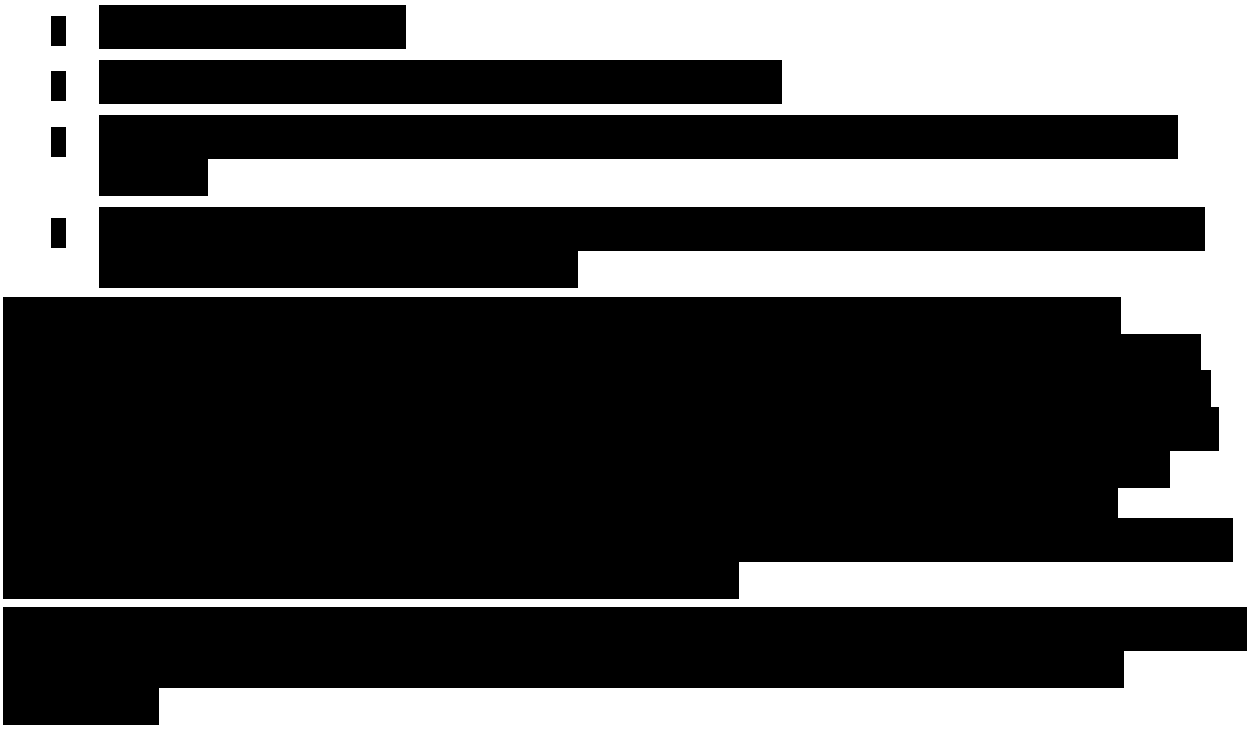
Temperature, heart rate, blood pressure, and respiratory rate measured after the subject has been seated for 10 minutes

6.2.15 Women of Childbearing Potential

To be considered not of childbearing potential, a woman must be postmenopausal with amenorrhea for at least 1 year prior to Screening and documented follicle-stimulating hormone level in the postmenopausal range or must have undergone one of the following sterilization procedures at least 180 days before the first IP dose:

- hysteroscopy sterilization (with a copy of the confirmation test)
- bilateral tubal ligation or bilateral salpingectomy
- hysterectomy
- bilateral oophorectomy





6.3 Screening Period

6.3.1 Visit 1: Screening

Subjects will be screened to assess eligibility criteria within 21 days before Baseline (first dose of IP). The following procedures will be performed:

- Written informed consent. Subjects will consent to participation in the study and all study procedures by signing the study informed consent form (ICF).
- Demographics and disease characteristics (including use of CFTR modulators such as ivacaftor or lumacaftor, use of dornase alfa, history of *P aeruginosa* colonization, number of pulmonary exacerbations in the last 12 months, date of last pulmonary exacerbation, chronic azithromycin use, CFTR genotype)
- Medical history, including medication use
- Complete physical exam
- 12-lead ECG
- Height and weight, calculation of BMI
- Vital signs
- Pulse oximetry
- Spirometry

- Collection of blood samples:
    - hematology
    - serum chemistry
    - serum pregnancy test for women of childbearing potential
    - HIV antibody, hepatitis C virus antibody, and hepatitis B surface antigen assays
- Collection of urine samples:
    - urinalysis
    - alcohol and drug screen

No study specific X-ray is required. If X-rays are available for subjects, they should be reviewed for any evidence of significant lung abnormalities (e.g., major atelectasis or pneumothorax).

Subjects on cyclical inhaled antibiotic (e.g. tobramycin, amikacin) treatments should be scheduled for the Baseline visit such that they are about midway in the cycle of administration of the inhaled antibiotics on the day of the Baseline visit.

The subject will be scheduled for the next visit, informed of the estimated length of the visit, and instructed to eat breakfast before the visit, take concomitant medications per Section 6.2.10.

6.4 Treatment Period

6.4.1 Visit 2: Baseline (Within 21 days of Screening)

The following procedures will be performed before IP administration:

- Interim medical history
- Recording of information about concomitant medications
- Focused physical exam
- 12-lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Administration of CFQ-R (must be performed before spirometry and collection of sputum, blood, and urine samples)
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Sputum induction and sample collection (must be performed after spirometry)
- Collection of blood samples:

- hematology
- serum chemistry (includes hs-CRP)

- Collection of urine samples:
  - urinalysis
  - urine pregnancy test for women of childbearing potential (review results before randomization)

Upon determination that a subject meets all inclusion and no exclusion criteria, the subject will be randomized to the treatment assignment via an IWRS.

[redacted]

IP will be dispensed to the subject, and the first dose of IP will be taken at the investigational site with a full glass of water (about 250 mL or 8 oz). The subject will be observed in the clinic for 4 hours after IP administration.

[redacted]

Vitals signs will be measured and recorded before discharge.

Information about any AEs that occurred after IP administration will be recorded.

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast before the visit, take the IP with breakfast before the visit [redacted] and take concomitant medications per Section 6.2.10.

[redacted]

6.4.2 Visit 3: Week 4 (28 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam

- 12-lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis
    - urine pregnancy test for women of childbearing potential (review results before administering or dispensing of IP)

[redacted]

For the subjects who are to be administered the IP in the clinic, the dose of IP will be taken at the investigational site with a full glass of water (about 250 mL or 8 oz).

IP will be dispensed and the subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast before the visit, take the IP with breakfast before the visit [redacted] and take concomitant medications per Section 6.2.10.

[redacted] If the subject takes the IP at home, he/she should be instructed to note the time of dosing.

6.4.3 Visit 4: Week 6 (42 Days ± 5 Days After Visit 2)

- Recording of information about any AEs and concomitant medications
- Collection of blood samples:
    - serum chemistry

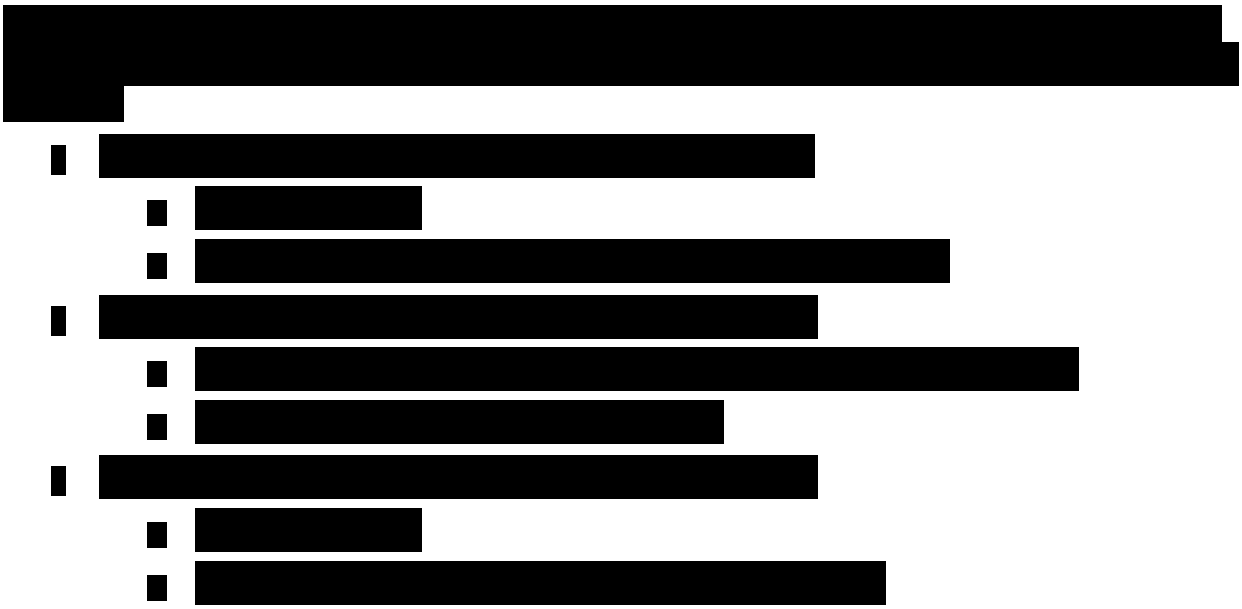
For purposes of this visit, local laboratories may be used at the discretion of the site investigator if travel to the site presents a hardship to the subject. If a local laboratory test value is found to be abnormal and clinically significant, it should be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If a subject is unable to travel to the site due to hardship, recording of information about any AEs and concomitant medications should be done by telephone.

6.4.4 Visit 5: Week 8 (56 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- 12-lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Sputum induction and sample collection (must be performed after spirometry)
- Collection of blood samples:

  - hematology
  - serum chemistry (includes hs-CRP)
- Collection of urine samples:
  - urinalysis
  - urine pregnancy test for women of childbearing potential (review results before administering or dispensing of IP)



For the subjects who are to be administered the IP in the clinic, the dose of IP will be taken at the investigational site with a full glass of water (about 250 mL or 8 oz).

IP will be dispensed and the subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast and take the IP with breakfast before the visit, and take concomitant medications per Section 6.2.10..

6.4.5 Visit 6: Week 12 (84 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- 12 lead ECG

- Weight
- Vital signs
- Pulse oximetry
- Administration of CFQ-R (must be performed before spirometry and collection of blood and urine samples)
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis
    - urine pregnancy test for women of childbearing potential (review results before dispensing of IP)
- Dispensing of IP

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast and take the IP with breakfast before the visit, and take concomitant medications per Section 6.2.10.

6.4.6 Visit 7: Week 16 (112 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- Weight
- Vital signs
- Pulse oximetry
- Spirometry

- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - serum chemistry
- Collection of urine samples:
    - urine pregnancy test for women of childbearing potential (review results before dispensing of IP)
- Dispensing of IP

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and to eat breakfast and take the IP with breakfast before the visit and take CF medications before the visit.

6.4.7 Visit 8: Week 20 (140 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- Weight
- Vital signs
- Pulse oximetry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - serum chemistry
- Collection of urine sample:
    - urine pregnancy test for women of childbearing potential (review results before dispensing of IP)
- Dispensing of IP

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast and take the IP with breakfast before the visit, and take concomitant medications per Section 6.2.10.

6.4.8 Visit 9: Week 24 (168 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- 12-lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Administration of CFQ-R (must be performed before spirometry and collection of sputum, blood, and urine samples)
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Sputum induction and sample collection (must be performed after spirometry)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis
    - urine pregnancy test for women of childbearing potential (review results before dispensing of IP)
- Dispensing of IP (2 bottles)

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit (phone call) and informed of the estimated length of the call.

6.4.9 Visit 10: Week 28 (196 Days ± 5 Days After Visit 2)

The following procedures will be performed during a **phone call** from the site to the subject:

- Recording of information about any AEs and concomitant medications
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- If a pulmonary exacerbation is suspected, the subject must visit the clinic for further assessment (history, physical examination, and tests as determined by the Investigator) to determine whether a pulmonary exacerbation has occurred.
- The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast and take the IP with breakfast before the visit, and take concomitant medications per Section 6.2.10. (

6.4.10 Visit 11: Week 32 (224 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- 12-lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis

  - urine pregnancy test for women of childbearing potential (review results before dispensing of IP)

- Dispensing of IP (2 bottles)

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit (phone call) and informed of the estimated length of the call.

6.4.11 Visit 12: Week 36 (252 Days ± 5 Days After Visit 2)

Same as Visit 10 (Section 6.4.9)

6.4.12 Visit 13: Week 40 (280 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Focused physical exam
- 12 lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis
    - urine pregnancy test for women of childbearing potential (review results before dispensing of IP)
- Dispensing of IP (2 bottles)

The subject will be instructed to take the IP with a full glass of water (about 250 mL or 8 oz) at about the same time every day with breakfast.

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit (phone call) and informed of the estimated length of the call.

6.4.13 Visit 14: Week 44 (308 Days ± 5 Days After Visit 2)

Same as Visit 10 (Section 6.4.9)

Subjects on cyclical inhaled antibiotic (e.g. tobramycin, amikacin) treatments should be scheduled for the next visit (Week 48) such that they are about midway in the cycle of administration of the antibiotics on the day of the visit.

6.4.14 Visit 15: Week 48 (336 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Collection of IP from previous study visit and count of capsules
- Recording of information about any AEs and concomitant medications
- Complete physical exam
- 12-lead ECG
- Weight
- Vital signs
- Pulse oximetry
- Administration of CFQ-R (before spirometry and collection of sputum, blood, and urine samples)
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Sputum induction and sample collection (must be performed after spirometry)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis
    - urine pregnancy test for women of childbearing potential

The subject will be instructed to contact the site if she/he has any symptoms suggestive of a pulmonary exacerbation.

The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast before the visit, and take concomitant medications per Section 6.2.10.

6.5 Follow-Up Period

6.5.1 Visit 16: Week 52 (364 Days ± 5 Days After Visit 2)

The following procedures will be performed:

- Recording of information about any AEs and concomitant medications
- Focused physical exam
- Weight
- Vital signs
- Pulse oximetry
- Spirometry
- Pulmonary exacerbation checklist per modified Fuchs criteria (recorded directly in the eCRF)
- Collection of blood samples:
    - hematology
    - serum chemistry (includes hs-CRP)
- Collection of urine samples:
    - urinalysis
    - urine pregnancy test for women of childbearing potential

7 SUBJECT AND STUDY DISCONTINUATION

Subjects who terminate the study early after randomization may not be replaced, regardless of the reason for withdrawal.

7.1 Screen Failures

Subjects who sign and date the ICF but who do not meet the eligibility criteria (Section 4) or who decide not to move forward with the Baseline visit are defined as screen failures. Each Investigator will maintain a screening log that lists all subjects screened and any reasons for screen failure. A copy of this log will be retained in the Investigator's study files.

7.2 Premature Discontinuation

Any subject who becomes pregnant during the study must be immediately and permanently discontinued from study treatment.

[redacted]

In addition, a subject may be prematurely discontinued from study treatment for any of the following reasons:

- AE
- Subject noncompliance or unwillingness to comply with the procedures required by the protocol
- Protocol violation (e.g., violation of eligibility criteria or receipt of the incorrect IP or dose)
- Investigator discretion
- Sponsor request

Any subject who discontinues from study treatment for any reason should not be withdrawn/discontinued from the study and should complete the remaining study visits.

Pulmonary exacerbations can occur in the patient population being studied. In case of a pulmonary exacerbation, the subject should be continued on the IP unless she/he takes a prohibited concomitant medication (Section 5.9), or, in the opinion of the Investigator, should be discontinued from study treatment in view of being medically unstable.

Subjects who discontinue IP for any reason (including because of an AE) should not be withdrawn/discontinued from the study and should complete remaining study visits. If IP is discontinued, it may be restarted at the discretion of the investigator after discussion with the medical monitor.

All subjects are free to withdraw/discontinue from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals/discontinuations from the study. The reason for the subject's

withdrawal/discontinuation from the study will be specified in the source documents. Subjects who withdraw/discontinue from the study should be encouraged to visit the clinic for an Early Termination visit; the procedures to be performed at this Early Termination visit are detailed in the Schedule of Events (Appendix 1).

7.3 Study or Site Termination

Conditions may arise during the study that could prompt the Sponsor to halt the study or to terminate study conduct at a study site. Conditions that may prompt such considerations include, but are not limited to, the following events:

- The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of Sponsor to suspend, discontinue, or shorten the study
- Failure of the Investigator to enroll eligible subjects into the study
- Failure of Investigator to comply with International Conference of Harmonisation Tripartite Guideline: Guideline For Good Clinical Practice E6 (R1) (ICH-GCP) guidelines or applicable regulations
- Submission of false information from the research facility to the Sponsor, a monitor, a Regulatory Authority, or an Institutional Review Board/Ethics Committee (IRB/EC)
- Insufficient adherence to protocol requirements
- A conflict of interest for the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial
- The Institution or IRB/EC under for-cause investigation by a Regulatory Authority

8 ADVERSE EVENTS

8.1 Reporting Responsibilities

AEs will be reported for each subject from the signing of the study ICF through study completion or early termination. It is the responsibility of the Investigator to assess the severity and causality of all AEs and whether or not the event began before or after initiating study treatment. Data describing AEs will be entered in the subject's medical record and eCRF, and as appropriate, in an SAE report. SAEs will be reported to the Sponsor as described in Section 8.6.

Subjects who experience AEs, whether or not serious, should receive appropriate treatment and medical supervision as clinically indicated. All AEs must be followed until resolution, stabilization, or a time that is mutually agreed upon between the Medical Monitor and the Investigator.

8.2 Definitions

8.2.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with this product. For purposes of this trial, AEs will be reported from the signing of the study ICF through study completion or early termination. A TEAE is an AE that occurs after the first dose of IP.

8.2.2 Serious Adverse Event

An AE is considered serious if, in the opinion of either the Investigator or the Sponsor, it meets any of the following criteria:

- Results in death
- Is life-threatening (an AE is considered life-threatening if, in the opinion of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/capacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

If it is not certain that an event meets the above definitions of an SAE, the Investigator should contact the Medical Monitor to discuss.

8.2.3 Severity Assessment

The Investigator will assess the severity of each AE according to the following criteria:

- **Mild (Grade 1):** awareness of signs or symptoms but easily tolerated and are of minor irritant type. Symptoms do not require therapy or a medical evaluation. Signs and symptoms are transient.
- **Moderate (Grade 2):** events that introduce a low level of inconvenience or concern to the subject but are usually improved by simple therapeutic measures. Moderate experiences may cause some interference with function.
- **Severe (Grade 3):** events that generally require systemic drug therapy or other treatment. They are usually incapacitating.

8.2.4 Causality Assessment

The Investigator will assess causality of each AE in accordance with the following definitions:

- **Not related:** The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject. This is especially so when an event occurs prior to the commencement of treatment with the IP.
- **Unlikely:** The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or a concomitant drug administered to the subject and does not follow a known response to the IP.
- **Possible:** The event follows a reasonable temporal sequence from the time of IP administration or follows a known response to the IP but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.
- **Probable:** The event follows a reasonable temporal sequence from the time of IP administration and follows a known response to the IP and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.
- **Definite:** The event follows a reasonable temporal sequence from the time of IP administration and follows a known response to the IP and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject and in addition one or more of the following:
    - Occurs immediately following IP administration
    - Improves on stopping the IP
    - Reappears on repeat exposure to the IP

8.2.5 Assessment of Expectedness

Each SAE considered to be possibly, probably, or definitely related to the IP must be assessed for expectedness to determine whether it is reportable as a SUSAR (Suspected Unexpected Serious Adverse Reaction). The Reference Safety Information for this study, against which expectedness assessments are made, can be found in the IB. Determination of the expectedness of an event is the responsibility of the Sponsor.

8.3 Clinical Laboratory Abnormalities

Any laboratory abnormality deemed clinically significant by the Investigator will reported as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Screening/Baseline so that in the judgment of the Investigator an alteration in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis (e.g., anemia) should be reported as the AE term. Repeated additional tests or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

8.4 Physical Exam Abnormalities

Any physical exam abnormality deemed clinically significant by the Investigator at Screening or Baseline will be reported as medical history. Any physical exam abnormality emergent after the administration of IP, or abnormality that has worsened since Screening or Baseline reporting, that is deemed clinically significant by the Investigator, will be reported as an AE.

8.5 Pregnancy

A subject who becomes pregnant during the trial must discontinue IP use. All pregnancies in female subjects that occur during the trial must be reported to the Sponsor and followed to conclusion. The outcome of each pregnancy must be reported on the Pregnancy Report Form.

Pregnancy alone is not an AE, nor is an induced elective abortion to terminate a pregnancy without medical reason. However, an induced therapeutic abortion to terminate a pregnancy because of complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion is always considered an SAE.

8.6 Reporting of Serious Adverse Events

SAEs must be reported to the Sponsor or designee within 24 hours of awareness of the event. If at the time the Investigator submits an initial SAE report the event has not resolved, the Investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing). All SAEs must be followed until resolution, stabilization, or a time that is mutually agreed upon between the Medical Monitor and the Investigator.

An SAE report should be sent to the Sponsor's designee:

After review of the initial SAE report, additional documentation (e.g., clinic or hospital records, or procedure reports) may be requested

8.7 Reporting to Regulatory Authorities and Institutional Review Boards/Ethics Committees

Reporting of AEs, including SUSARs, will be carried out in accordance with applicable regulations.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size

The sample size calculation was performed with the following assumptions:

- 1:1:1 ratio of 50 mg CTX-4430, 100 mg CTX-4430, and placebo
- Differences between average treatment effect of 50 mg/100 mg CTX-4430 and placebo response of 3.5 units at 48 weeks
- Common standard deviation (SD) of 7 units
- Power of at least 90%
- One-sided alpha = 0.05

A sample size of 156 subjects (52:52:52) is required on the basis of the above assumptions for the primary, overall comparison of CTX-4430 versus placebo. Although the primary analysis will be based upon the Full Analysis Population (FAP), it is also of interest to be able to have a sufficient number of subjects to support analyses in the Per-protocol Population (PP). It is expected that approximately 80% of randomized subjects will be included in the PP. As such, the number of randomized subjects is increased to 195 (65:65:65).

9.2 Analysis Conventions

The primary efficacy analysis will be based upon an average over the 2 doses of CTX-4430 with testing at a 1-sided 0.05 level of significance. If this comparison is significant, additional tests will be conducted. Analyses for other endpoints will use 2-sided tests at the 0.05 level.

Data collected in this study will be reported using summary tables and patient data listings. For categorical variables, frequencies, and percentages will be presented. For continuous variables, the number of subjects (n), mean, SD, median, minimum, and maximum will be presented. Unless otherwise indicated, confidence intervals will be 95% 2-sided intervals.

9.3 Subject Populations

- **Randomized Population:** All subjects randomized to an active treatment or placebo will be included in the Randomized Population. Subjects in the Randomized Population will be analyzed according to their randomized treatment group.
- **Full Analysis Population:** All subjects randomized to and receiving at least 1 dose of assigned treatment will be included in the FAP. Subjects in the FAP will be analyzed according to their randomized treatment group.
- **Safety Population:** All subjects randomized to and receiving at least 1 dose of assigned treatment will be included in the Safety Population. All safety analyses will be performed using the Safety Population according to the actual treatment received.
- **Per-Protocol Population:** Subjects in the FAP who met all study inclusion/exclusion criteria and have at least 80% of assigned treatment doses at the time of their 48 week

assessment will be included in the PP. All subjects in the PP will be analyzed according to the actual treatment received.

9.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics (including medical history and prior medications) will be summarized descriptively overall and by treatment group.

9.5 Subject Disposition

The number of screened subjects, screen failures, randomized subjects, treated subjects, subjects who completed the study, and subjects who discontinued the study will be summarized by treatment group. Reasons for discontinuation will also be summarized.

The number of subjects in each subject population and the reasons for inclusion in the FAP but not in the PP will be summarized by treatment group.

9.6 Analysis

9.6.1 Primary Efficacy Endpoint

The primary efficacy analysis of change from Baseline to Week 48 in FEV_1 percent predicted will be performed on the FAP. The primary efficacy evaluation will compare the combined, average absolute change from Baseline in FEV_1 percent predicted of the 50 mg and 100 mg CTX-4430 treatment groups versus the placebo group.

The primary analysis will be based upon an analysis of variance (ANOVA) in which the average of the Week 48 change from Baseline in FEV_1 for the 2 CTX-4430 doses is compared to that in the placebo group. The ANOVA model will contain a separate term for each dose group with the average over the 2 CTX-4430 doses created by averaging the parameters estimates from the ANOVA model. In addition to terms for treatment group, the ANOVA will include stratification for the factors used for randomization. For subjects missing their Week 48 assessment, the average placebo change from Baseline to Week 48 will be imputed. Descriptive statistics will be presented by treatment group and averaged CTX-4430 dose.

If the primary analysis (aggregate CTX-4430 effect) reaches the 0.05 level of significance (1-sided), the individual CTX-4430 doses will be compared to the placebo arm using Dunnett's procedure at the 0.05 (2-sided) alpha level. This procedure maintains the type I error at the usual 0.05 (2-sided) level for the individual dose comparisons with placebo while allowing a proof of concept test for the pooled comparison at the 0.05 (1-sided). This approach is consistent with the Fleming and Richardson approach to Phase 2 screening trials in which a screening trial, if positive at the more stringent 0.05 2-sided level after preliminary testing, can be treated as providing a more definitive statistical test and may reduce the amount of additional confirmatory trial data that is needed.[33]. No other adjustments for multiplicity will be used and other statistical analyses will be viewed as supportive.

Sensitivity analyses for the primary analysis will be conducted in which 1) the last available data is used (last observation carried forward), 2) the primary analysis is repeated using observed data only, and 3) using a rank based analysis where missing data are assigned the worst rank.[34]

In addition to the univariate ANOVA, a mixed model repeated measures analysis of change from Baseline in FEV_1 percent predicted at each post-Baseline visit using all available data will be used to explore the consistency of the treatment effect over time. The model will include treatment (all 3 doses), visit, and treatment-by-visit interaction with additional factors for the randomization strata.

The primary analysis will be repeated on the PP as a supportive analysis.

9.6.2 Secondary and Exploratory Endpoints

Clinical Endpoints

The spirometry-based secondary endpoints will be analyzed using the same methods as the primary endpoint. For time points prior to 48 weeks, only descriptive statistics will be presented.

Pulmonary exacerbations will be analyzed both as the time to first pulmonary exacerbation and the number of pulmonary exacerbations.

Biomarker Endpoints

The analyses of biomarkers (sputum DNA and elastase, serum hs-CRP) will be based upon descriptive statistics by treatment group. In addition to the basic descriptive statistics, confidence intervals for the differences between the CTX-4430 groups and placebo will be presented.

Exploratory Endpoints

Analyses of sputum bacterial density (*P aeruginosa*, *Burkholderia cepacia* complex*, Achromobacter xylosoxidans, Stenotrophomonas maltophilia, and Staphylococcus aureus* (including methicillin–resistant *S aureus* and small colony variants of *S aureus* [CFUs]) and HRQOL will be based upon descriptive statistics by treatment group. In addition to the basic descriptive statistics, confidence intervals for the differences between the CTX-4430 groups and placebo will be presented.

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9.6.3 Safety and Tolerability Endpoints

Extent of Exposure

Treatment exposure and treatment compliance will be summarized by treatment group.

Adverse Events

The Investigator's verbatim term for each AE will be mapped to system organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities.

TEAEs will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment. Subject counts and percentages and event counts will be presented for each treatment group and totaled for all treatment groups for the following:

- All TEAEs
- All TEAEs by severity

- All TEAE by relationship
- All SAEs
- TEAEs leading to discontinuation of study participation

Listings will be presented by subject for all TEAEs, all SAEs, TEAEs with death as the outcome, and TEAEs leading to discontinuation from the study.

Events recorded prior to the initiation of study treatment will be listed separately.

Concomitant Medications

Concomitant medications will be coded using the most current WHO Drug Dictionary and summarized by drug class and medication term with results presented by treatment group. A listing of prior and concomitant medications will also be presented.

Clinical Laboratory Evaluations

Clinical laboratory results at each time point and change from Baseline will be displayed using summary statistics (n, mean, SD, median, minimum and maximum values) by treatment group.

Listings of laboratory data will also be presented. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low. In addition, shift tables will be presented to display the shift in the normal range categories (low, normal, high) from Baseline to each specified time point. Baseline is defined as the latest result obtained prior to first IP administration.

Weight, Pulse Oximetry, Vital Signs, Electrocardiogram Parameters

Values at each time point and change from Baseline for weight, pulse oximetry, vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, and temperature), and ECG parameters will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each time point by treatment group. Baseline is defined as the latest result obtained prior to first IP administration. In addition, shift tables will be presented to display the shift in the normal range categories (abnormal/normal) from Baseline to each specified time point. Listings of these data will also be presented.

9.7 Interim Analysis by IDMC

An IDMC will be formed to periodically review (approximately every 8 weeks) the accumulating study data. The primary responsibility of the IDMC will be to monitor subject safety (including pulmonary exacerbations) and study conduct. The IDMC will have access to both safety and efficacy data. The IDMC will be requested to avoid formal evaluations of efficacy for the purpose of discontinuing the trial early for benefit. As such, no adjustment for multiple testing will be required. The IDMC will review the study data in accordance with a written charter.

10 ETHICAL AND ADMINISTRATIVE RESPONSIBILITIES

10.1 Ethical Conduct of the Study

The trial will be conducted in compliance with the protocol, applicable GCP standards/guidelines, and applicable regulations. The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor and the Investigators abide by ICH-GCP and applicable regulations. Compliance also constitutes compliance with the ethical principles that have their origins in the Declaration of Helsinki.

10.2 Institutional Review Board Approval

This protocol, ICFs, and any subsequent modifications to these documents will be reviewed and approved by the relevant IRB(s)/EC(s) responsible for oversight of the study. A letter from the IRB/EC indicating approval of the study to be conducted by the Investigator will be provided to the Sponsor before initiation of any enrollment at that site. All reviews and approvals by the IRB/EC will be in accordance with applicable regulations.

10.3 Informed Consent

The ICF must be signed and dated before performance of any study-related procedures. The original signed ICF for each subject must be filed with records kept by the Investigator. A copy of the ICF must be provided to the subject.

10.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study will be managed by the Investigator and the investigational site staff with adequate precautions to ensure the confidentiality of these data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor; the IRB(s)/EC(s) approving this research; and any applicable Regulatory Authorities will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and data without violating the subjects' confidentiality, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

10.5 Protocol Amendments

Any changes to the protocol will be made in writing by the Sponsor in the form of a protocol amendment. Except when necessary to eliminate immediate hazards to the subjects, changes will not be implemented until approval by the IRB/EC and Regulatory Authority, if required.

10.6 Case Report Forms

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained investigational site personnel. The eCRF will be signed by the Investigator or a Subinvestigator listed on Form FDA 1572. It is the responsibility of the Investigator to ensure the eCRFs are completed and submitted to the Sponsor (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change, and person making change).

10.7 Source Document Maintenance

Source documents are defined as the original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and IP accountability records. All source documents produced in this study will be maintained by the Investigators and made available for monitoring and audit by the Sponsor's representatives, and inspection by the IRB/EC or Regulatory Authorities.

10.8 Retention of Records

Each Investigator will maintain all study records and documents pertaining to the conduct of this study and the distribution of IPs (including, but not limited to, medical records, eCRFs, ICFs, and IP accountability records) in accordance with applicable regulations. No study records should be destroyed without authorization from the Sponsor.

10.9 Study Monitoring

Site monitoring visits will be conducted by an authorized Sponsor representative (the monitor) in accordance with ICH-GCP and applicable regulations. The monitor will review eCRFs, source documents, ICFs, and other study records to verify that the rights and well-being of subjects are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved version of the protocol, ICH-GCP, and applicable regulations.

10.10 Protocol Deviations

The Investigator is responsible for reporting protocol deviations to the IRB/EC in accordance with applicable regulations. Additionally, the following protocol violations will be reported in the eCRF:

- Violation of eligibility criteria
- Receipt of the incorrect IP or dose
- Receipt of a prohibited concomitant medication

10.11 Financial Disclosure

Investigators participating in this study will provide accurate financial disclosure information to the Sponsor as required by 21 Code of Federal Regulations Part 54. Investigators will update the financial information if any relevant changes occur during the study and for 1 year after completion of the study.

10.12 Publication and Disclosure Policy

Investigators and their staff shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Sponsor's products or research programs that is provided to the Investigator. All such persons must be instructed not to further disseminate this information to others. Investigators shall not use the Confidential Information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by the Investigator shall not apply to: (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than disclosure by or through the Investigator; (c) information which, as evidenced by the Investigator's written records, was known by the Investigator prior to Celtaxsys disclosure; (d) information which is lawfully disclosed to the Investigator by a third party not under any obligation of confidence to Celtaxsys; or (e) information which is required to be disclosed by law or government Regulatory Authority, provided reasonable advance notice of such disclosure is given to Celtaxsys.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Celtaxsys, Inc. Celtaxsys reserves the right of prior review of any publication or presentation of information related to the study. Celtaxsys may use these data now or in the future for presentation or publication at Celtaxsys' discretion or for submission to government Regulatory Authorities.

Celtaxsys adheres to the general principles of publication of scientific data as articulated by the International Committee of Medical Journal Editors and acknowledges its responsibility to publish results of clinical trials. Persons that fulfill the criteria for authorship (http://www.icmje.org/recommendations/) may be authors for publications on the basis of their contributions to the design, conduct, results, and/or analysis of this clinical trial. Investigators will have access to the data from this clinical trial for the preparation of scientific presentations and publications, in accordance with their institutional agreements with Celtaxsys, subject to the requirements of confidentiality. Celtaxsys reserves the right to review, within a reasonable time frame, results or analyses from data generated in this study that are intended for public presentation, including scientific meetings.

In signing this protocol, the Investigator agrees to the release of the data from this study and acknowledges the above confidentiality and publication policy. The provisions of this release shall survive the completion of the study.

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Appendix 1 Schedule of Events

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Early Term
Visit Name/Week[a]	Screening	Baseline	4	6	8	12	16	20	24	28	32	36	40	44	48	52	
Informed consent (study ICF [redacted])	X																
Demographics & disease characteristics	X																
Medical history	X	X															
Physical exam [c]	X[c]	X	X		X	X	X	X	X		X		X		X[c]	X	X
12-lead ECG	X	X	X		X	X			X		X		X		X		X
Height, calculation of BMI	X																
Weight	X	X	X		X	X	X	X	X		X		X		X	X	X
Vital signs	X	X[d]	X		X	X	X	X	X		X		X		X	X	X
Pulse oximetry	X	X	X		X	X	X	X	X		X		X		X	X	X
CFQ-R[e]		X				X			X						X		X
Spirometry	X	X	X		X	X	X		X		X		X		X	X	X
Pulmonary exacerbation checklist		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum sample [f]		X			X				X						X		X
Hematology	X	X	X		X	X			X		X		X		X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X		X		X		X	X	X
hs-CRP		X	X		X	X			X		X		X		X	X	X
Serum pregnancy test [g]	X																
HIV & HCV antibodies, HBsAg	X																
Urinalysis	X	X	X		X	X			X		X		X		X	X	X
Urine pregnancy test [g]		X	X		X	X	X	X	X		X		X		X	X	X
Urine alcohol and drug screen	X																
Randomization		X															
[redacted]		X[h]	X[h]		X[h]												
IP dispensing		X	X		X	X	X	X	X[i]		X[i]		X[i]				
IP collection and capsule count			X		X	X	X	X	X		X		X		X		X
AE & concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BMI = body mass index, CFQ-R = Cystic Fibrosis Questionnaire – Revised; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus, hs-CRP = high-sensitivity C-reactive protein: ICF = informed consent form; IP = investigational product; [redacted].

a Baseline visit within 21 days of Screening, window for other visits: ±5 days
b Visits 10, 12, and 14 will be conducted via phone call.
c Complete physical exam at Screening and Week 48, focused physical exam at all other visits
d Predose and before discharge
e To be administered before spirometry and sample collection
f After spirometry
g For women of childbearing potential
[redacted]
l 2 bottles of IP must be dispensed

Appendix 2 Protocol Amendments and Summary of Changes

Amendment 1, Protocol Version 2.0, 17 July 2015

The overall purposes of this amendment are as follows:

- Further specify organisms to be evaluated in sputum culture
- Provide a clearer definition for pulmonary exacerbation, consistent with the modified Fuchs criteria
- Shorten the requirement for stable exposure to CFTR modulators from 12 weeks to 8 weeks
- Clarify the time for reporting SAEs to the Sponsor
- Change the contact name for reporting SAEs to the Sponsor
- Revise safety evaluations and contraception requirements in response to comments for consideration from the US FDA (14 July 2015)

Amendment 2, Protocol Version 3.0, 05 September 2015

The overall purposes of this amendment are as follows:

- To align the protocol with the Reference Safety Information section in the revised version of the Investigator Brochure
- Clarify blinding and unblinding overview

Amendment 2, Protocol Version 3.1, 30 September 2015

The overall purposes of this amendment are as follows:

- Clarify the reasons for premature discontinuation of study treatment

A summary of changes is provided in the table following; deleted text is identified in strikethrough, and new text is identified in bold italics.

Amendment 3, Protocol Version 4.0, 19 November 2015

The overall purposes of this amendment are as follows:

- [redacted]
- To provide additional options for subjects on ivacaftor-lumacaftor combination given the unreliability of hormonal contraception for these subjects.
- Additional urine pregnancy tests to more closely monitor women of childbearing potential.
- Clarify Screening period and allow rescreening of subjects with approval of medical monitor.

- Further clarify the reasons for premature discontinuation of study treatment.
- Modified Exclusion Criteria:
  - Only excluding mycobacterium abscessus which is the species specifically associated with a more rapid decline in lung function.
  - [redacted]
  - Further clarification on exclusion of concurrent clinical trial participants.
- Changed storage temperatures of study drug to be consistent with stability data.

A summary of changes is provided in the table following; deleted text is identified in strikethrough, and new text is identified in bold italics

Amendment 4, Protocol Version 5.0, 04 May 2016

The overall purposes of this amendment are as follows:

- To clarify the tobacco inclusion criteria that any type of smoking is not permitted due to its adverse effects on pulmonary function.
- The drug screen exclusion criteria was modified to allow for investigator judgement in the case of a positive drug screen with prescription medications or therapeutic use of marijuana
- The colonization exclusion criteria was modified to allow for subjects who have multiple negative cultures within the past year to be included.
- To remove the exclusion for montelukast and other 5-LO inhibitors that are not in the same leukotriene pathway as CTX-4430. Some of these agents are very commonly used by CF patients and should have no impact on the study.
- Abstinence was added as a form of acceptable contraception since it is a highly effective form of contraception that is used by many young women with CF. Requiring another form of contraception adds unnecessary risk. Double barrier and barrier plus spermicide forms of contraception were added for subjects at the discretion of the investigator.
- The time following completion of another clinical trial has been reduced from 60 to 30 days to be consistent with studies in this therapeutic area.
- To clarify that subjects whose spirometry fails quality criteria do not screen fail, but can be retested once within 7 days. At other visits, the investigator can use his discretion to repeat spirometry that fails quality criteria

A summary of changes is provided in the table following; deleted text is identified in strikethrough, and new text is identified in bold italics.

Amendment 1, Protocol Version 2.0, 17 July 2015 Summary of Changes Table

Section	Changed Text	Rationale
Title Page	[redacted]	Personnel change, area code change
Synopsis, Study Design	***Study Design:***	Clarification
Synopsis, Study Design 3.1 Study Design	A blood sample will be collected before the first dose and at Weeks 4, 8, 12, 24, ***32, 40,*** 48, and 52 for measurement of hs-CRP.	FDA comments for consideration
Synopsis, Study Design 3.1 Study Design	Hematology, serum chemistry, and urinalysis will be evaluated at Screening, before the first dose and at Weeks 4, 8, 12, 24, ***32, 40,*** 48, and 52.	FDA comments for consideration
Synopsis, Study Design 3.1 Study Design	A 12-lead electrocardiogram (ECG) will be performed at Screening, before the first dose and at Weeks ***4,*** 8, 12, 24***, 32, 40,*** and 48.	FDA comments for consideration
Synopsis, Criteria for Evaluation	**Bacterial Density:** presence/absence ***and quantitative counts (CFUs)*** of bacteria in sputum: *Pseudomonas aeruginosa*, ***Burkholderia cepacia complex, Achromobacter xylosoxidans, Stenotrophomonas maltophilia, and Staphylococcus aureus (including*** methicillin–resistant ~~*Staphylococcus*~~ ***S*** *aureus* and ~~other bacteria~~ ***small*** colony ~~counts (CFUs) in sputum~~ ***variants of S aureus)***	Further specification of organisms to be evaluated in sputum culture
1.1 Cystic Fibrosis	The most recent advance in the treatment of CF is ~~correction or~~ modulation of the abnormal CFTR protein. Currently, ivacaftor is the only CFTR therapy approved for the treatment of CF.[17] It is indicated only for the small percentage of CF patients (approximately 6%) who have the G551D and functionally similar gating mutations. Trials with correctors and ~~modulators~~ ***potentiators*** for other classes of CFTR genetic mutations (such as ataluren) and with combinations of correctors and ~~modulators~~ ***potentiators*** (such as the ivacaftor/lumacaftor combination [18]) are ongoing. However, even these targeted therapies may not address the dysregulated inflammatory response, as exemplified by the GOAL study.[19]	Clarification and addition of references

Section	Changed Text	Rationale
3.2.3 Study Endpoints	Pulmonary exacerbations are defined ~~by~~ ***as treatment with oral, inhaled, or intravenous (IV) antibiotic(s) for ≥4 of symptoms/signs per*** the criteria of Fuchs et al (modified Fuchs criteria) the standard definition used in clinical trials of CF	Clarification
4.1 Inclusion Criteria	7. If on ivacaftor or ivacaftor-lumacaftor combination, on a stable regimen for at least ~~3 months~~ ***8 weeks*** before Baseline	Based on Phase 3 data for either ivacaftor or the combination of ivacaftor-lumacaftor, the peak effect on FEV_1 occurs within 8 weeks of treatment, and no additional improvement is seen with further therapy.
4.1 Inclusion Criteria	18. Females of childbearing potential must have a negative pregnancy test at Screening (unless surgically sterile) and must agree to use ***a highly*** effective contraception method~~s~~ from screening throughout the duration of ***the*** study ~~treatment~~ (refer to Section 5.9.2 for definition of ***highly*** effective methods).	In consideration of the FDA comments for consideration regarding contraception in women of childbearing potential
4.2 Exclusion Criteria	4. History of ***either*** alcoholism or drug abuse within 2 years before Screening 5. Positive alcohol ~~and~~ ***or*** drug test at Screening	Clarification
5.9.2 Contraception	Women of childbearing potential must use a~~n~~ ***highly*** effective method of contraception until 28 days after taking the last dose of IP. ***Highly e***~~E~~ffective methods of contraception include the following methods: monogamous relationship with vasectomized partner, licensed hormonal methods ***associated with inhibition of ovulation (e.g., combination oral contraceptive pills, progestin-only hormonal contraception that inhibits ovulation) or intrauterine devices (including intrauterine hormonal systems)*** ~~monogamous relationship with vasectomized partner, licensed hormonal methods (e.g., oral contraceptive pills) or intrauterine devices, or a barrier method (e.g., condom, diaphragm) with spermicide~~.	In consideration of the FDA comments for consideration regarding contraception in women of childbearing potential

<table>
<tr><th>Section</th><th>Changed Text</th><th>Rationale</th></tr>
<tr><td>6.1 Blood Sample Volume
Table 3 Total Blood Volume Collected from Subjects During the Study</td><td>
<table>
<tr><th>Sample Type</th><th>Number of Sampling Time Points</th><th>Volume per Time Point</th><th>Total Volume</th></tr>
<tr><td>Screening laboratory tests…..</td><td>1</td><td>~ 15 mL</td><td>~ 15 mL</td></tr>
<tr><td>Hematology</td><td>9 <s>7</s></td><td>~ 10 mL</td><td>~ 90 <s>70</s> mL</td></tr>
<tr><td>Serum chemistry (including hs-CRP)</td><td>9 <s>7</s></td><td>~ 5 mL</td><td>~ 40 <s>35</s> mL</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">Total blood volume</td><td>~ 200 <s>170</s> mL</td></tr>
</table>
</td><td>Increased number of samples per FDA comments for consideration</td></tr>
<tr><td>6.2.8 Pulmonary Exacerbation Checklist</td><td><s>Components of the modified Fuchs criteria for pulmonary exacerbation will be evaluated by completing a checklist:</s>
<s>• Treatment with oral, inhaled, or intravenous antibiotic(s)</s>
Pulmonary exacerbations are defined as treatment with oral, inhaled, or IV antibiotic(s) for ≥4 of symptoms/signs listed below per the modified Fuchs criteria. The pulmonary exacerbation checklist will capture the signs/symptoms listed below as well as the treatment with oral, inhaled, or IV antibiotics:</td><td>Clarification</td></tr>
<tr><td>6.4.2 Visit 3: Week 4 (28 Days ± 5 Days After Visit 2)
6.4.9 Visit 10: Week 32 (224 Days ± 5 Days After Visit 2)
6.4.11 Visit 12: Week 40 (280 Days ± 5 Days After Visit 2)</td><td>• 12-lead ECG</td><td>FDA comments for consideration</td></tr>
<tr><td>6.4.9 Visit 10: Week 32 (224 Days ± 5 Days After Visit 2)
6.4.11 Visit 12: Week 40 (280 Days ± 5 Days After Visit 2)</td><td>• Collection of blood samples:
o hematology
o serum chemistry
• Collection of urine samples:
o urinalysis</td><td>FDA comments for consideration</td></tr>
<tr><td>8.6 Reporting of Serious Adverse Events</td><td>SAEs must be reported to the Sponsor or designee within <s>1 business day</s> 24 hours of awareness of the event.</td><td>Clarification</td></tr>
</table>

Section	Changed Text	Rationale
8.6 Reporting of Serious Adverse Events	[redacted] After review of the initial SAE report, ~~the Medical Monitor may request additional documentation (e.g., clinic or hospital records, or procedure reports).~~***additional documentation (e.g., clinic or hospital records, or procedure reports) may be requested.***	Delegation of safety function
9.6.2 Secondary and Exploratory Endpoints	Analyses of sputum bacterial density (*P aeruginosa*, methicillin-resistant *Staphylococcus aureus*, ~~and other bacteria colony counts [CFUs]~~) ***Burkholderia cepacia complex, Achromobacter xylosoxidans, Stenotrophomonas maltophilia, and Staphylococcus aureus [including methicillin–resistant S aureus and small colony variants of S aureus (CFUs)]*** and HRQOL will be based upon descriptive statistics by treatment group.	Further specification of organisms to be evaluated in sputum culture
11 References	***17. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365:1663-1672.*** ***18. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med. 2015. May 17. [Epub ahead of print].***	New references added
Appendix 1 Schedule of Events	[ECG and sample collection time points added in accordance with changes in Sections 6.4.2, 6.4.9, and 6.4.11]	FDA comments for consideration

Amendment 2, Protocol Version 3.0, 05 September 2015 Summary of Changes Table

Section	Changed Text	Rationale
1.2.2, Clinical Trials of CTX-4430	***Headache was the most common adverse event considered by the investigators to be related to the use of CTX-443 (13%).***	VHP recommendation, clarification on expected AEs
5.6, Blinding and Unblinding	~~Unblinding of treatment assignment is discouraged. In the event of a medical emergency for which the identity of the treatment assignment is critical to the care of a subject the Investigator should call the Medical Monitor to discuss unblinding. In the event that unblinding is deemed necessary, the treatment assignment will be provided to the Investigator via the IWRS. A decision to discontinue a subject from further IP administration is not a rationale to unblind the treatment assignment~~ ***All Celtaxsys study team staff members and contract research organization study team members will remain blinded unless specifically designated as unblinded and independent from the study team. Such independent, unblinded study personnel may include drug distribution and IWRS vendor staff. Pharmacovigilance staff will be unblinded as necessary for reporting to regulatory authorities, with appropriate controls to assure that access to any unblinded information is restricted to the safety reporting staff. The sponsor will maintain a list of any designated individuals at the vendors or sponsor that are designated as unblinded.*** ***The investigator will ensure that blinding is broken only in accordance with the protocol conditions for unblinding due to medical necessity or safety reasons.*** ***In the case of a medical emergency, where the appropriate treatment of the subject requires knowledge of the IP, CTX-4430 or placebo, the investigator may break the randomization code at any time for an individual subject through the IWRS system. Detailed procedures to break the blind will be provided to the investigator. In such cases, the AE necessitating the emergency blind break will be clearly justified, explained in writing, captured on the SAE form (if due to a SAE) in accordance with the procedures indicated in section 8.6., and must be reported to the medical monitor immediately.***	VHP recommendation, further clarification on blinding and unblinding
Cover Page/Headers/Footers	Update version number and date	Administrative changes/version control

Amendment 2, Protocol Version 3.1, 30 September 2015 Summary of Changes Table

Section	Changed Text	Rationale
7.2, Premature Discontinuation	***Any subject who becomes pregnant during the study must be immediately discontinued from study treatment.*** ***In addition,*** ~~A~~ ***a*** subject may be prematurely discontinued from study treatment~~, but not necessarily from the study,~~ for any of the following reasons: • AE • Subject noncompliance or unwillingness to comply with the procedures required by the protocol • Protocol violation (e.g., violation of eligibility criteria or receipt of the incorrect IP or dose) • ~~Pregnancy~~ • Investigator discretion • Sponsor request ***Any subject who discontinues from study treatment for any reason should not be withdrawn/discontinued from the study and should complete the remaining study visits.***	VHP recommendation, further clarification on reasons for discontinuing study treatment
Cover Page/Headers/Footers	Update version number and date	Administrative changes/version control

Amendment 3, Protocol Version 4.0, 19 November 2015 Summary of Changes Table		
• **Section**	• **Changed Text**	• **Rationale**
Cover Page	[redacted]	EudraCT number added per EU Requirement
Cover Page/Headers/Footers	Update version number and date	Administrative changes/version control
Table of Contents	***Visit 4: Week 6 (42 Days ± 5 Days After Visit 2)*** ***5.5 Screening*** ***5.10.3 Contraception in women on ivacaftor-lumacaftor combination*** [redacted]	Updated to match protocol
Synopsis Study Design	Hematology, ~~serum chemistry,~~ and urinalysis will be evaluated at Screening, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, 48, and 52. ***Serum chemistry will be evaluated at Screening, before the first dose and at Weeks 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, and 52.***	Added Serum Chemistry to a new Week 6 Visit and to the 16 and 20 Week Visits [redacted]
List of Abbreviations	***GGT - Gamma-glutamyltransferase***	Updated List
[redacted]	[redacted]	[redacted]
3.1 Overall Study Design	[redacted]	
3.1 Overall Study Design	Hematology, ~~serum chemistry,~~ and urinalysis will be evaluated at Screening, before the first dose and at Weeks 4, 8, 12, 24, 32, 40, 48, and 52. ***Serum chemistry will be evaluated at Screening, before the first dose and at Weeks 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, and 52.***	Added Serum Chemistry to a new Week 6 Visit and to the 16 and 20 Week Visits [redacted]
4.2 Exclusion Criteria	7. Positive culture for Burkholderia cepacia complex or Mycobacterium ***abscessus*** ~~species~~ within 24 months before Screening or between Screening and Baseline	Only excluding mycobacterium abscessus which is the species

	11. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) **>**2 □ the upper limit of normal (ULN) at Screening [redacted] ***20.*** Participation in a clinical trial for any medical***/device*** product within 60 days before Screening or between Screening and Baseline ***(participation in a noninterventional or observational study is permitted)***	specifically associated with a more rapid decline in lung function. [redacted] Further clarification on exclusion of concurrent clinical trial participants.
Section 5.4 Storage	IP***s*** should be stored in the containers in which they are supplied at controlled room temperature ***(***15°C to ~~***30***~~***25°C /*** 59°F to ~~***86***~~***77°F)***, and protected from ultraviolet light.	Changed storage temperatures to be consistent with the IP stability data.
Section 5.5 Screening	***The Screening Period will occur within 21 days before the first dose of study drug to confirm that subjects meet the selection criteria for the study. The assessments to be conducted are shown in 6.3.1. The investigator (or an appropriate authorized designee) will obtain informed consent from each subject.*** ***Rescreening:*** ***Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated. Subjects may only be rescreened once. If a subject is rescreened, the screening window begins at that time.***	Clarifies Screening period and may allow rescreening of subjects with approval of medical monitor.
5.7 Blinding and Unblinding	***The Sponsor medical team, for matters relating to safety concerns and associated regulatory reporting, may unblind individual subjects at any time.***	Clarifies role of sponsor medical team on unblinding
5.10.3 Contraception in women on ivacaftor-lumacaftor combination	***In female subjects of childbearing potential who are receiving ivacaftor-lumacaftor combination therapy, hormonal contraception is considered to be unreliable and hence cannot be used as a highly effective method of contraception. These study subjects must either use another method of highly effective contraception from the list above (section 5.10.2), or one of these following two alternative methods of contraception:*** ***1) For women who are continuing a hormonal method of contraception, or willing to begin using one, one of the following barrier methods of contraception should be added;*** ***a. Male condom*** ***b. Diaphragm***	Added section to provide additional options for subjects on ivacaftor-lumacaftor combination given the unreliability of hormonal contraception for these subjects.

<table>
<tr><td></td><td>c. Cervical cap
d. Female condom
2) In women who are not on a hormonal method of contraception, one of the following methods of contraception should be used.
a. Double barrier methods of contraception which is the use of a male condom, plus either diaphragm or cervical cap. The male condom cannot be used with a female condom as a double barrier method of contraception due to risk of tearing
b. Male or female condom plus a spermicide, or diaphragm plus a spermicide (acceptable methods if spermicide is regionally available)
If local regulations require the use of additional contraceptive measures, these must be followed.</td><td></td></tr>
<tr><td>6.1 Blood Sample Volume Table 3</td><td><table>
<tr><th>Sample Type</th><th>Number of Sampling Time Points</th><th>Volume per Time Point</th><th>Total Volume</th></tr>
<tr><td>Screening laboratory tests…..</td><td>1</td><td>~ 15 mL</td><td>~ 15 mL</td></tr>
<tr><td>Hematology</td><td>9</td><td>~ 10 mL</td><td>~ 90 mL</td></tr>
<tr><td>Serum chemistry (~~including~~ may include hs-CRP)</td><td>~~9~~12</td><td>~ 5 mL</td><td>~ ~~45~~ 60 mL</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">Total blood volume</td><td>~ ~~200~~ 215 mL</td></tr>
</table></td><td>Adjusted Blood Volumes based on added serum chemistry tests.</td></tr>
<tr><td>6.2.8 Pulmonary Exacerbation Checklist</td><td>The date of onset of the pulmonary exacerbation will be recorded, which will be defined as the date of initiation of antibiotics for the pulmonary exacerbation.</td><td>Clarified documentation of the starting date of any Pulmonary Exacerbation.</td></tr>
<tr><td>6.2.9 Serum Chemistry</td><td>Albumin, alkaline phosphatase, ALT, AST, GGT, bicarbonate, bilirubin (total and direct), blood urea nitrogen, calcium, chloride, creatinine, glucose, phosphorus (phosphate), potassium, sodium, uric acid, total protein, and hs-CRP</td><td>Added GGT to the liver function test panel.</td></tr>
<tr><td>6.2.11 Sputum Induction and Sample Collection</td><td>The subject will be given 2 sterile jars of adequate volume to collect the sputum. ~~The filled jars with lids will be weighed and recorded. Every effort should be made to use the same study scale for weighing filled jars with lids.~~</td><td>Removed requirement to weigh jars of sputum at the site as this will be performed at the central laboratory.</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

		
6.4 Treatment Period 6.4.2, 6.4.5, 6.4.6, 6.4.7, 6.4.8, 6.4.9, 6.4.11, 6.4.13	***o urine pregnancy test for women of childbearing potential (review results before administering or dispensing of IP)***	Additional urine pregnancy tests to more closely monitor women of childbearing potential.
6.4 Treatment Period 6.4.1, 6.4.2, 6.4.4, 6.4.5, 6.4.8, 6.4.10, 6.4.12, 6.4.14, 6.5.1	***o*** serum chemistry ***(includes hs-CRP)***	To clarify that the serum chemistry sample will be used to measure hs-CRP at these visits.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
7.2 Premature Discontinuation	Any subject who becomes pregnant during the study must be immediately ***and permanently*** discontinued from study treatment. [redacted]	Clarified that pregnant women will be permanently discontinued from study drug. [redacted]
7.2 Premature Discontinuation	Subjects who discontinue IP for any reason (including because of an AE) should not be withdrawn/discontinued from the study and should complete remaining study visits. ***If IP is discontinued, it may be restarted at the discretion of the investigator after discussion with the medical monitor.***	To clarify that any restarting of study drug will occur only after consultation between the Investigator and the medical monitor.
8.5 Pregnancy	The outcome of each pregnancy must be reported on the ***Pregnancy Report Form*** ~~eCRF~~.	Correction on the mode of reporting.
8.6 Reporting of Serious Adverse Events	[redacted]	Correction of email address.
[redacted]	[redacted]	[redacted]

	[redacted] **Created separate row for hs-CRP** **Renumbered Visits that will be conducted via phone call**.	

Amendment 4, Protocol Version 5.0, 04 May 2016 Summary of Changes Table		
• **Section**	• **Changed Text**	• **Rationale**
Cover Page/Headers/Footers	Update version number and date	Administrative changes/version control
List of Abbreviations	***ATS – American Thoracic Society*** ***ERS – European Respiratory Society***	Updated List
4.1 Inclusion Criteria	***12. No smoking (including electronic cigarettes) for at least 6 months before Screening and agreement not to use such products for the duration of the study*** ~~12. No use of tobacco or nicotine-containing products for at least 6 months before Screening and agreement not to use such products for the duration of the study~~	Modified language to focus on exclusion of smoking.
4.1 Inclusion Criteria	13. Females of childbearing potential must have a negative pregnancy test at Screening (unless surgically sterile) and must agree to use a~~n highly~~ effective contraception method from screening throughout the duration of the study (refer to Section 5.10.2 for definition of ~~highly~~ ***acceptable*** effective methods)	See rationale for Section 5.10.2 below
4.2 Exclusion Criteria	4. History of either alcoholism or drug abuse ***in the opinion of the investigator*** ~~within 2 years before screening~~	Added language to allow the investigator to use clinical judgement based on the knowledge of the subject
4.2 Exclusion Criteria	5. ~~Positive alcohol or drug test at Screening.~~	To allow the investigator to use results of the drug/alcohol screen at the screening visit, along with knowledge of the subject, to guide their decision on exclusion # 4.
4.2 Exclusion Criteria	***6. 6. Colonization with organisms associated with a more rapid decline in respiratory function in CF patients (e.g. all Burkholderia species, Mycobacterium abscessus). Subjects with a history of a positive culture could be considered free of colonization if she/he has had 6 subsequent respiratory tract cultures negative for these bacteria within the past 24 months prior to Screening, with one of these cultures obtained within 6 months prior to Screening*** ~~Positive culture for Burkholderia cepacia complex or Mycobacterium abscessus within 24 months before Screening or between Screening and Baseline~~	To allow patients to enter the study if they have had negative cultures after an initial positive culture

4.2 Exclusion Criteria	11. Bilirubin >1.25 x ULN at Screening. ***Subjects with known Gilbert's syndrome can be included with bilirubin >1.25 x ULN***	Subjects with Gilbert's syndrome can have elevated bilirubin in the absence of liver pathology
4.2 Exclusion Criteria	17. Use of ~~a 5-lipoxygenase (5-LO) inhibitor (e.g., zileuton), leukotriene receptor antagonists (e.g. montelukast, zafirlukast),~~ systemic corticosteroids, or systemic ~~antibiotic~~ ***antimicrobial*** therapy (other than chronic ***antimicrobial use, e.g.*** azithromycin, flucloxacillin, itraconazole~~ use for CF~~) within 14 days before Screening or between Screening and Baseline	Rationale: 5 lipoxygenase inhibitors and leukotriene receptor antagonists are commonly used in patients with CF. Mechanistically, they are distinct from a LTA-4 hydrolase inhibitor like CTX-4430, and should not interfere with study assessments. Patients could be concomitantly on chronic antimicrobials. The intent of this exclusion is to exclude patients who could be acutely unstable and in need of treatment with systemic antimicrobials
4.2 Exclusion Criteria	19. Participation in a clinical trial for any medical/device product within ~~60~~ ***30*** days before Screening ~~or between Screening and Baseline~~ (participation in a noninterventional or observational study is permitted)	Rationale: To facilitate participation of subjects with a rare disease in clinical trials
5.5 Screening	***Based on investigator's judgement, borderline abnormal laboratory tests which may exclude the subject, may be repeated once within 7 days of the screening visit without the subject being considered a screen fail. The medical monitor must be consulted for approval in such cases.*** ***In addition, subjects who fail to meet the ATS/ERS criteria for quality (acceptability, reproducibility, and end of test criteria) at screening may be retested once without being considered a screen failure. This retest should occur at least one day after the initial screening visit and should be completed within 7 days of the original screening visit date. Final decision on screen failure will be based upon FEV1 data after review with the medical monitor.***	To allow the investigators to use clinical judgement in repeating borderline lab tests For repeat spirometry, see rationale for Section 6.2.10 below
5.9 Concomitant Medications	~~Use of 5-LO inhibitors, leukotriene receptor antagonists, c~~Chronic use of systemic corticosteroids, and regular use (>3 times per week) of high-dose NSAIDs (e.g., >1.6 g ibuprofen/day) is prohibited during the study….	See explanation of Exclusion Criteria 18 above

5.10.2 Contraception	1. Monogamous relationship with vasectomized partner, 2. Licensed hormonal methods associated with inhibition of ovulation (e.g., combination oral contraceptive pills, progestin-only hormonal contraception that inhibits ovulation) o ***For women who are receiving ivacaftor-lumacaftor combination therapy, hormonal contraception, including oral, injectable, transdermal and implantable, is considered to be unreliable and hence cannot be used as an effective method of contraception. In such patients who are on hormonal contraception, one of the following barrier methods of contraception should be added; male condom, diaphragm, cervical cap or female condom.*** ***3. Intrauterine contraceptive devices (including intrauterine hormonal systems).*** ***4. True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject, can be considered an effective method of contraception based on the judgement of the investigator. Periodic abstinence is not an acceptable method of contraception.*** ***Based on the investigator's judgement, the following acceptable methods of contraception may also be used:*** ***1. Double barrier methods of contraception, which is the use of a male condom plus either diaphragm or cervical cap, may be allowed. The male condom cannot be used with a female condom as a double barrier method of contraception due to risk of tearing.*** ***2. Male or female condom plus a spermicide, or diaphragm plus a spermicide may be allowed (acceptable methods if spermicide is regionally available)*** ***If local regulations require the use of additional contraceptive measures, these must be followed.*** ~~Contraception in women on ivacaftor-lumacaftor combination~~ ~~In female subjects of childbearing potential who are receiving ivacaftor-lumacaftor combination therapy, hormonal contraception is considered to be unreliable and hence cannot be used as a highly effective method of contraception. These study subjects must either use another method of highly effective contraception from the list above (section 5.10.2), or one of these following two alternative methods of contraception:~~ ~~1) For women who are continuing a hormonal method of contraception, or willing to begin using one, one of the following barrier methods of contraception should be added;~~ ~~a. Male condom~~	In the CF population, there are abstinent patients who are unwilling to initiate contraceptive measures. True abstinence is regarded as a highly effective form of contraception when in line with the preferred and usual lifestyle. In the prior version of the protocol, contraceptive methods were added for women who are on ivacaftor/lumacaftor combination therapy. These methods may be acceptable based on investigator judgement for other subjects given they are effective methods of contraception. In nonclinical reproductive toxicity studies, oral doses of CTX-4430 equivalent to 680 mg/day in humans did not exhibit adverse effects on fertility, implantation, pregnant females, or embryofetal development.

	~~b. Diaphragm~~ ~~c. Cervical cap~~ ~~d. Female condom~~ ~~2) In women who are not on a hormonal method of contraception, one of the following methods of contraception should be used.~~ ~~a. Double barrier methods of contraception which is the use of a male condom, plus either diaphragm or cervical cap. The male condom cannot be used with a female condom as a double barrier method of contraception due to risk of tearing~~ ~~b. Male or female condom plus a spermicide, or diaphragm plus a spermicide (acceptable methods if spermicide is regionally available)~~ ~~If local regulations require the use of additional contraceptive measures, these must be followed.~~	
5.11 Compliance	An investigational site staff member will count the capsules returned by each subject at Visits 3, 5 to ~~8~~***9***, ***11***~~10~~, ~~12~~***13***, and ~~14~~ ***15*** and record the number of capsules returned. Subjects will be questioned in relation to any capsules which may have been lost or destroyed to gain a full understanding of the number of capsules taken during the treatment period.	Corrected based on addition of Week 6 visit in Amendment 3
6.2.10 Spirometry	Spirometry will be performed before the sputum induction procedures. ***Subjects should take their concomitant medications as per their usual schedule. However, any short-acting bronchodilator (e.g. albuterol) should not be taken within 4 hours of scheduled time for spirometry, and any long-acting bronchodilator should not be taken within 12 hours (e.g. salmeterol) or 24 hours (e.g. tiotropium bromide) of scheduled time for spirometry.*** ~~The timing will be such that the subject has taken CF medications, including inhaled medications, approximately 4 hours before spirometry.~~ ***Subjects who fail to meet the ATS/ERS criteria for quality (acceptability, reproducibility, and end of test criteria) at screening may be retested once without being considered a screen failure. This retest should occur at least one day after the initial screening visit and should be completed within 7 days of the original screening visit date. For other visits, if a subject fails to adhere to protocol requirements, (e.g. bronchodilator use) or fails to meet ATS/ERS criteria for quality, then at the discretion of the investigator, the spirometry may be repeated once. The retest should occur at least one day after the initial visit but as soon as possible up to a maximum of 7 days.***	Focus is now only on those medications which would have an impact on spirometry measures Clarifies that subjects who fail to meet ERS/ATS quality criteria can be retested once.
6.3 Screening 6.4 Treatment Period 6.4.1, 6.4.2, 6.4.4, 6.4.5, 6.4.7, 6.4.9, 6.4.14	The subject will be scheduled for the next study visit, informed of the estimated length of the visit, and instructed to eat breakfast before the visit, take the IP with breakfast before the visit [redacted] ***and*** take ~~CF~~ concomitant medications per Section 6.2.10. ~~(including inhaled medications)~~	Harmonized language with Section 6.2.10

	~~approximately 4 hours before spirometry is scheduled, and not to take any long-acting beta-agonist within 12 hours before spirometry.~~	
6.4.11, 6.4.13	Same as Visit ~~9~~ **10**	Corrected based on addition of Week 6 visit in Amendment 3
Attachment	Previous version of the protocol, Version 4.0 Amendment 3, November 19, 2015 was submitted via paper submission to FDA and is now being submitted via electronic submission as an attachment to this protocol.	